VOLUME 11 NUMBER 3

*July • 1956*

# JOURNAL OF GERONTOLOGY

## *Contents*

### Section A—Biological Sciences and Clinical Medicine

PAGE

METACOLLAGEN AS THE APPARENT ELASTIN ... *Ilona Banga, Joseph Baló, and Desiderius Szabó* 242

BASEMENT MEMBRANES, GROUND SUBSTANCE, AND LYMPHOCYTIC AGGREGATES IN AGING ORGANS ... *Sheldon C. Sommers* 251

TREATMENT OF SENESCENT MALE RATS WITH CORTISONE ACETATE ALONE OR TOGETHER WITH SEX AND THYROID HORMONES ... *V. Korenchevsky* 261

PERITONEAL FLUID MAST CELLS: THEIR NUMBERS AND MORPHOLOGY IN RATS OF VARIOUS BODY WEIGHTS (AGES) ... *Jacques Padawer and Albert S. Gordon* 268

HEXOSAMINE AND ACID-HYDROLYZABLE SULFATE CONCENTRATIONS OF THE AORTA AND PULMONARY ARTERY IN INDIVIDUALS OF VARIOUS AGES ... *J. E. Kirk and M. Dyrbye* 273

SOME BIOCHEMICAL ASPECTS OF AGING IN INSECTS ... *Morris Rockstein* 282

NEUROHYPOPHYSEAL RESPONSIVENESS IN THE NORMAL AND SENESCENT RAT ... *Sydney M. Friedman, J. A. M. Hinke, and Constance L. Friedman* 286

OBSERVATIONS ON BLOOD VESSELS AND EXERCISE ... *Clark E. Brown, T. C. Huang, Edward L. Bortz, and Clive M. McCay* 292

AGING: A THEORY BASED ON FREE RADICAL AND RADIATION CHEMISTRY ... *Denham Harman* 298

GERIATRIC PRACTICE: GERIATRIC OFFICE GYNECOLOGY ... *John C. Weed* 301

BOOK REVIEWS ... 307

### Section B—Psychological and Social Sciences, and Social Work and Administration

PROBLEM SOLVING SET IN DIFFERENT AGE GROUPS ... *Howard J. Heglin* 310

AN AGE DIFFICULTY IN SEPARATING SPATIALLY CONTIGUOUS DATA ... *Hilary M. Clay* 318

THE EFFECT OF MIGRATION ON THE NUMBER AND DISTRIBUTION OF THE AGED IN FLORIDA ... *Irving L. Webber* 323

THE ROLE OF WELFARE AGENCIES IN PROVIDING SERVICES TO THE AGED: THE ROLE OF THE PUBLIC AGENCY ... *Wilbur J. Cohen* 328

AGE AND ACHIEVEMENT: A CRITIQUE ... *Wayne Dennis* 331

REPLY TO DENNIS' CRITIQUE OF AGE AND ACHIEVEMENT ... *Harvey C. Lehman* 333

BOOK REVIEWS ... 338

### Section C—Index to Current Periodical Literature

INDEX TO CURRENT PERIODICAL LITERATURE ... 340

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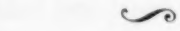

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# JOURNAL OF GERONTOLOGY

VOLUME 11, NUMBER 3
JULY, 1956

## Section A

## Biological Sciences and Clinical Medicine

JOURNAL OF GERONTOLOGY

VOLUME 11, SECTION A JULY, 1956 NUMBER 3

# METACOLLAGEN AS THE APPARENT ELASTIN

ILONA BANGA, Ph.D., JOSEPH BALÓ, M.D., AND DESIDERIUS SZABÓ, M.D.

*(From the First Department of Pathological Anatomy and Experimental Cancer Research, Medical University, Budapest, Hungary)*

A theory has been recently advanced by Hall, Keech, Reed, Saxl, Tunbridge, and Wood (15) referring to the transformation of collagen fibers into elastin. The experimental bases of this theory are the observations of Burton, Hall, Keech, Reed, Saxl, Tunbridge, and Wood (10) that collagen fibers isolated from the skin as well as collagen fibers within the skin become similar to elastin under treatment with alkaline borate buffer and sodium metaperiodate (pH 5). The similarity is demonstrable histologically in so far as collagen fibers become stainable with Hart's modification of Weigert's stain. In the electron microscopic picture structureless, branching fibrils appear similar to elastin as a continuation of striated collagen fibrils, among which a lot of amorphous material can be seen. This proves that the elastic fibers and amorphous material increase as a result of the transformation of collagen fibers. The extract obtained with borate buffer contains such proteins of which the hydroxyproline content is higher than that of collagen. On the basis of all these proofs collagen has apparently been transformed into elastin. According to the opinion of Hall and associates both elastic and collagen fibers are products of fibroblasts which by special selection of polypeptides and polysaccharides build up each of the fibers. This would be the way to the normal production of elastin. Under pathologic circumstances the elastic fibers are formed from the products of the partial hydrolysis of the collagen fibers.

Since this theory disregards the possibility of other special cells besides fibroblasts taking part in the formation of elastic fibers, and, in addition, the theory neglects some recent data in the literature concerning the complex character of the collagen, we will discuss some pertinent data in the literature.

The origin of elastic fibers has been discussed for more than 50 years by histologists. Loisel (22) considered three theories regarding the origin of elastic fibers: 1.) Elastic fibers are formed without the activity of cells from a basic substance as a result of some particular arrangement; 2.) They arise from protoplasm activity directly, or by way of transformation; 3.) They originate from the activity of the nucleus only.

Loisel (22), after a detailed study of the elastic fibers of the cervical ligaments of mammals beginning from the embryonic state up to adult age, established the fact that cells play a part in the origin of the elastic fibers and of the granular elastin. He called these cells elastogenes or elastoblasts. It is interesting that in his summary (p. 187) he states that elastic fibers are first formed from granules and that later connective tissue elements which can be found between the elastic fibers are transformed into elastic material; this transformation is the result of a continuous vascular atrophy.

Krompecher (20) studied the origin of elastic fibers of the blood vessel wall from the embryo stage until adult age. He attaches importance in their formation to some peculiar cells, the elastoblasts.

Baló (1) stated that by administration of ammonium hydroxide to rabbits acidosis could be produced. As a consequence of the acidosis elastic fibers in the aorta and in other arteries are destroyed. In the case of less severe acidosis, a kind of mucoid is accumulated, as a result of which the elastic fibers break into granules. This transformation is followed by the regeneration of the elastic fibers which reorient the injured fibers of the media. In places where this

Submitted for publication January 12, 1956.

occurs groups of cells can be found which produce elastic material. Baló (2) produced arteriosclerosis in rabbits not only by ammonium hydroxide but also by thyroxine. In the blood vessel wall of such animals intimal proliferation can be observed between the lamina elastica interna and the endothelium. Oval and spindle-shaped cells accumulate here among which a network of fine elastic fibers develops. Thus Baló's studies prove that some special cells must play an important role in the regeneration of elastic fibers.

Ranke (28) was the first to suggest the theory of impregnation according to which a fiber or membrane can be stained either with acid fuchsin or resorcin-fuchsin, depending on whether it is impregnated with collagen or with elastin. This theory was further developed by Hueck (18), who pointed out that it has never yet been proved that the so-called pure collagen or elastic fibers really consist only of collagen or elastin, chemically speaking. On the other hand, as he states (p. 340), it is much easier to find proofs (11, 27) that collagen and elastic fibers or membranes do not consist of a single homogeneous material, but are mixtures of at least 2-3 components. This fact, which was pointed out by Hueck (18) more than 35 years ago, can now be proved by modern biochemical research.

The complex nature of collagen and elastic material became the focal point in the course of recent investigations. The electron-microscope study of collagen (13, 17, 29) has shown in a convincing manner that the cross-striation of the collagen fibers and the varying width of striation (200 A, 650 A, 2000-4000 A), the "fibrous long-spacing" and "segment long-spacing" structures, depend on the glycoprotein and nucleotide contents of the collagen. These components can be found in the alkaline phosphate extract of connective tissue.

Tustanovskii and associates (31) threw new light upon the relation of procollagen to collagen. They extracted the procollagen from the skin according to the method described by Orekhovich and associates (24) and called the residual insoluble collagen collastromin. The collastromin could not be stained with picrofuchsin and showed structureless formations in the electron microscope, i.e., it consisted of threads which have no cross-striation. According to the authors the procollagen is responsible for the staining of collagen by picrofuchsin as well as for its characteristic x-ray diagram and for its cross-striated structure found electronmicroscopically. They further pointed out that procollagen may be present in various forms (fibers, gel, monodisperse solution, and needle-shaped crystals). The procollagen formations are oriented on surfaces possessing free electric charge and thus cross-striations of various Å distances are formed. While Schmitt and associates (29) hold the mucoproteins and nucleotides soluble in alkali responsible for the cross-striated structure of collagen, according to Tustanovskii and associates (31) procollagen is responsible for the characteristic electron-microscopic picture.

Harkness and associates (16) and Jackson and Fessler (19) consider the alkali-soluble collagen isolated from the skin as the direct precursor of collagen and not the protein soluble in Orekhovich's citrate (23). Harkness and associates (16) found significant difference in the hydroxyproline and tyrosine contents of alkali-soluble and insoluble collagen. Jackson and Fessler (19) pointed out that the alkali soluble collagen is not homogenous, but that a so-called "heat-precipitated" collagen can be isolated from it. The latter corresponds to the procollagen of Orekhovich (23). According to this research alkali dissolves both mucoproteins and procollagen.

In our laboratory we have been working for many years with elastin and collagen. In the present paper different experiments are reported which prove that collagen fibers can be transformed into a substance which resembles elastin or seems to be the same as elastin in several respects.

## EXPERIMENTAL

During our investigations we realized that in studying the genesis, transformation, and degeneration of collagen fibers we should use material which contains the collagen fibers pure and free from other tissues. Fixed and embedded sections are not suitable because the collagen fibers react with most of the fixatives (formol, alcohol, acetone) and lose their native condition. It is therefore necessary to work with fresh, untreated substances. The most suitable is the collagen fiber isolated from the tail of rodents (mice, rats) or kangaroos. For the experiments below, pure collagen fibers, taken from the tail of 4-6 months old rats, cleaned with wet gauze and dried at 18 C. were used. Under the light microscope these fibers seem to be homogenous.

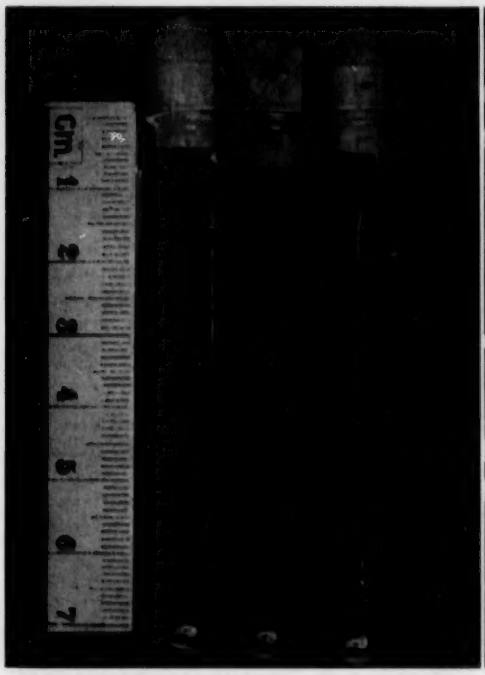


Fig. 1. In the first tube the native, in the second the contracted, and in the third the relaxed collagen (rat tail tendon) is to be seen. Tubes contain 40 per cent potassium iodide solution.

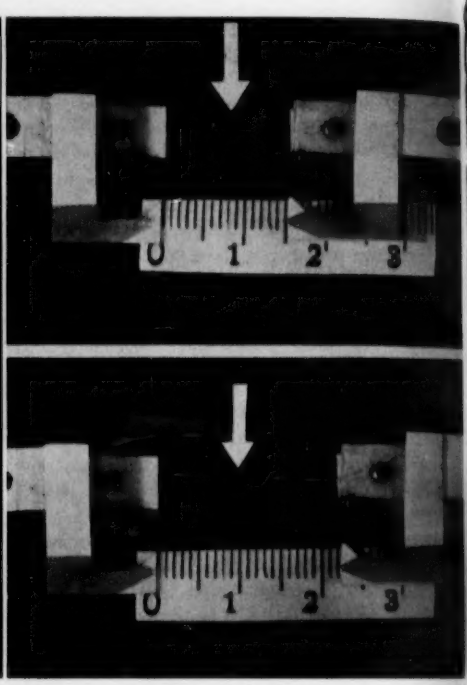


Fig. 2. In the thread-stretching-instrument a white arrow shows the metacollagen fiber. Figures demonstrate the elasticity and expansible character. In the picture above a fiber of 15 mm. length is shown, which in the picture below was extended to 22 mm.

TRANSFORMATION OF COLLAGEN FIBERS INTO A SUBSTANCE SIMILAR TO ELASTIN

In our previous studies (4, 7, 8) we showed that during thermohydral contraction (at 67 C.) or chemical contraction-relaxation (which takes place in 40 per cent potassium iodide solution at 20 C.) a mucopolysaccharide and a soluble protein similar to the procollagen of Orekhovich (23) are dissoved. The collagen fiber left behind after the dissolution of the two substances we called metacollagen. The metacollagen keeps its fibrous form but differs in its properties from the native collagen fibers. Its preparation in the purest form is as follows:

1. *Preparation of metacollagen with hydrothermal relaxation.*—The single native collagen fiber is loaded with lead shot weighing 80-100 times more than the fiber and immersed in water at 67 C. After 8-10 sec. the thermal contraction takes place in which the fiber shortens to 60-70 per cent of its original length. The thermal contraction is followed by thermal relaxation, during which the fiber regains its original length. Immediately afterwards the metacollagen fiber is removed from the hot water and placed in cold water and is subsequently dried in air.

2. *Preparation of metacollagen with chemical relaxation.*—The native loaded fiber (see above) is placed in 40 per cent potassium iodide solution at 20 C. The contraction and subsequent relaxation take place in a similar manner to that of thermal contraction-relaxation. But here the time is prolonged and in general the fibers reach maximal relaxation only after 20-30 min. The metacollagen fiber is washed in water and dried (fig. 1).

3. *Preparation of metacollagen by means of extraction.*—The native collagen fiber is extracted with phosphate buffer at pH 7.4 for three days in order to remove the mucoproteins. Following this it is extracted for 5-6 days with pH 4 citrate buffer at 37 C. under sterile conditions. The greater part of the procollagen dissolves during this time. In order to bring the

Fig. 3. Effect of elastase upon metacollagen fiber. Where elastase comes into contact with the fiber it breaks into fibrils.

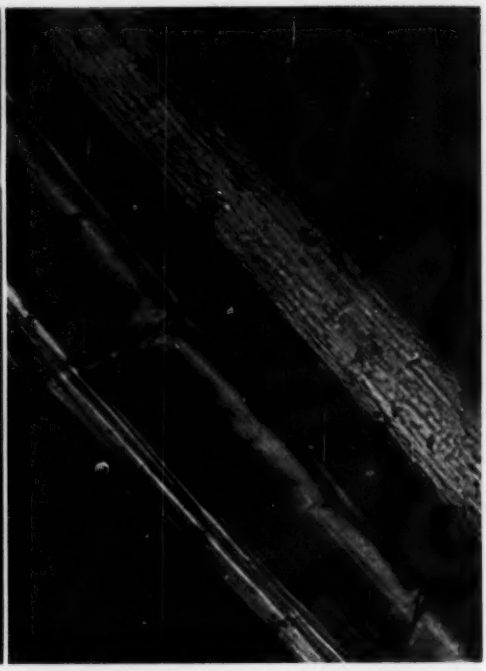

Fig. 4. Phenol reaction of collagen and metacollagen fiber. Left native collagen, right extended metacollagen fiber photographed in polarized light by insertion of gypsum plate. On the effect of phenol the metacollagen (right) is not changed, but the native fiber (left) is swollen and its positive birefringence is beginning to turn to negative.

procollagen completely into solution we extracted with distilled water at 50 C. for one hour longer. The fiber thus obtained resembles the metacollagen fiber prepared by means of method 2. This third method is much slower and does not always give satisfactory results. If we work with fiber of rats less than 4 months old, it loses much of its stability after such long treatment, unlike the collagen fibers of older rats.

In the following paragraphs we shall enumerate those properties in which the metacollagen is similar to elastin fiber.

1. *Elasticity.*—The metacollagen is elastic in water. If it is dried in stretched condition it keeps its extended form, but upon being put in water contracts again. Its elastic behavior is therefore like that of the elastic fiber (fig. 2).

2. *Double refraction.*—The metacollagen fiber, unlike native collagen fiber, shows no double refraction. Being stretched in a wet state it becomes birefringent. The double refraction of stretched and dried metacollagen remains high in lipoid solvents and oils (xylol, toluol, olive oil, cedar oil) like that of the elastin fiber. Exactly contrary to this is the behavior of the native collagen fiber, of which the well-known imbibition curve demonstrates the lowest values in the above mentioned substances concerning their refraction index (about 1.5). The metacollagen, similar to elastin, loses its double refraction in water and in watery solution when the previously stretched fiber contracts again. The most typical characteristic of the elastic fiber is likewise that it has birefringence in water only when stretched. This can be traced back to the fact that the elastin fiber as well as metacollagen fiber possesses only formal birefringence, which disappears in water by means of binding water molecules.

3. *Digestion by elastase.*—The metacollagen is digested by elastase. The dissolved substance,

called collagenolysate (5), contains the same reducing substance as the elastolysate (fig. 3).

4. *Phenol reaction.*—The phenol reaction discovered by Ebner in 1894, reverts the positive birefringence of collagen fiber into a negative one. The metacollagen fiber does not exhibit the phenol reaction characteristic of the collagen fiber. The elastic fiber similarly does not exhibit the phenol reaction. Therefore both the metacollagen and elastic fibers behave similarly with regard to the phenol reaction (fig. 4).

5. *Electron microscope studies.**—The metacollagen fiber in the electron microscope does not show any cross-striated structure like that of the collagen fiber, but it displays partly amorphous and partly membrane-like structures (fig. 5).

6. *Acid swelling.*—The metacollagen fiber, in contrast to native collagen fiber, does not swell in the presence of dilute acid. It does not even swell or dissolve in 0.01M acetic acid. In these properties also it agrees with the elastin fiber.

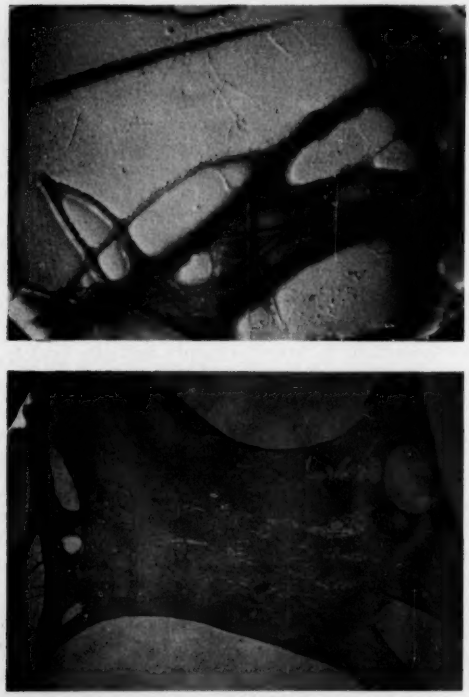

Fig. 5. Electron microscope pictures of metacollagen. It is in part transformed to membrane-like structure.

7. *Staining property.*—Metacollagen is stained with Weigert's resorcin-fuchsin (fig. 6). The native collagen fiber cannot be stained with this stain.

In some quantitative measurements concerning the resorcin-fuchsin binding capacity of metacollagen fibers we found that 170 mg. of metacollagen prepared according to method 3 binds 9 mg. resorcin-fuchsin, which amounts to 5.5 per cent. In contrast to this, native collagen fiber does not bind any demonstrable quantity of resorcin-fuchsin. Metacollagen does not stain with van Gieson's picrofuchsin, but it stains with congo red, contrary to native collagen fiber.

On the basis of these data, the conclusion could be drawn that Hall and associates (10) were correct when they claimed that collagen fiber could be transformed into elastin. But there are facts which are against this conclusion. One of these is the result of quantitative amino acid determination by paper chromatography.* Such analysis failed to show any significant difference between collagen and metacollagen. In contrast to this we were able to demonstrate a different amino acid composition of collagen and metacollagen by means of the silver nitrate method of Grassmann and Kusch (12). Measurements performed by this technique revealed that metacollagen, like pure elastin prepared from lig. nuchae or aorta, scarcely binds silver. While native collagen binds 12 mg. Ag/Gm., metacollagen binds only 3 mg. Ag/Gm. Likewise elastin prepared according to the method of Stein and Miller (30) binds 3 mg. Ag/Gm.

The metacollagen fiber differs from the collagen fiber in that two of the latter's components, mucoid, which dissolves in alkaline buffer, and the procollagen, are missing from the former. According to our experiments these two components are indispensable to the function of collagen fiber, which manifests itself in doing work measured by the shortening of the weighted fiber (6). Mucoid is dissolved during the contraction, and the dissolution of procollagen takes place while the fiber goes over from the contracted phase to the relaxed one (7, 8).

* These studies have been carried out in the Electron Microscope Institute of the Hungarian Academy of Sciences.

* We are indebted to B. Kell for carrying out the amino acid analysis.

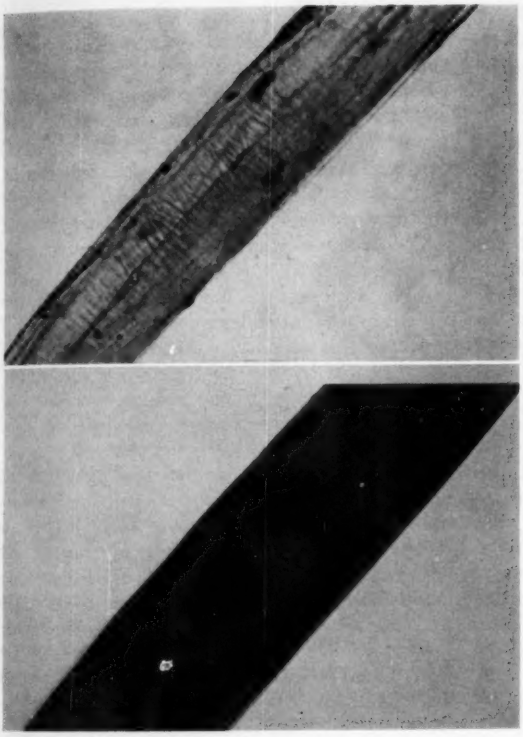

Fig. 6. Weigerts' resorcin-fuchsin stain. In the top illustration the native collagen fiber is not stained, contrary to the metacollagen fiber (lower picture), which is stained.

Metacollagen, as shown by our experiments, still contains a mucoid, which, however, has different properties from the mucoid which is dissolved from the fiber during contraction. This metacollagen mucoid can be hydrolyzed by the enzyme which we named elastomucase. On this basis it is similar to the mucoid of pure elastin.

STUDIES OF COLLAGEN FIBERS TREATED WITH BORATE BUFFER (pH 7-10) AND SODIUM METAPERIODATE SOLUTION (pH 5).

With alkaline borate buffer or phosphate buffer a mucoid or a part of a mucoid is dissolved from the collagen fiber. It is known that borate reacts with substances having two hydroxyl groups in orthoposition. The treatment with borate buffer using the method of Hall and associates (15) disintegrates the collagen fiber. This is exhibited both in electron micrograph, where elastin-like structures formed by the modification of collagen fibrils can be seen, and in the capacity of binding more Hart's modification of Weigert's stain than the native collagen fiber. We can confirm the observation of Burton and associates (10) and Hall and associates (15) that the collagen fiber can be converted to elastin-like material which is demonstrable by Weigerts' resorcin-fuchsin stain. But only a part of the collagen is converted to elastin. According to our theory concerning the structure of the collagen fiber, this modified collagen cannot be regarded as being identical with elastin fiber, because during treatment with borate it becomes only partly elastic. It stains with van Gieson's picrofuchsin, shows but diminished chemical contraction, and does not dissolve without residue in elastase. The collagen fiber of young animals disintegrates more easily and loses its stability; therefore is not suitable to work with.

The sodium metaperiodate solution (at pH 5) has apparently similar but not the same effect as borate buffer solution. The studies of Lhotka (21) show that metaperiodate is capable of splitting not only the 1-2 glycol and 1-2 hydroxylamino linkages but also it reacts with a number of amino acids. Whether or not in native collagen fiber sodium metaperiodate exerts its effect on glycol linkages of the polysaccharides or on the hydroxylamino or other amino acids cannot be stated definitely. It is clear from our experiments, however, that while the buffer solutions of organic acids (acetate, citrate) between pH 4-5 have the effect of breaking the links between metacollagen and procollagen in native collagen fiber, the metaperiodate solution strengthens these bonds. So the metaperiodate treated collagen fiber is a pseudoelastin fiber, which is similar to elastin in that it shows some elasticity and has no longer a swelling capacity in acids. Such fiber is similar to native collagen fiber too in that it shows hydrothermal and chemical contraction. It is, however, unable to relax, which in accordance with our theory, proves the hypothesis that the procollagen, as a result of the effect of metaperiodate solution, is bound so strongly to metacollagen that it cannot be liberated with the method used in our experiments (high temperature or 40 per cent potassium iodide solution). Our studies related to collagen structure (8) show that the hydro-

thermal contraction is always followed by hydrothermal relaxation—just as the chemical contraction is followed by relaxation if the procollagen can dissolve from the fiber. In a future publication we shall discuss the question of whether the collagen fiber of old animals is incapable of chemical relaxation simply because the procollagen cannot be dissolved.

The experiments above indicate that collagen fiber treated with borate buffer and sodium metaperiodate contains procollagen; therefore with these substances the conversion of collagen fiber into elastin fiber is not complete. In order that collagen fiber should resemble elastin fiber in all respects it is necessary that besides the polysaccharide component the procollagen component also be dissolved.

Following the heat treatment of Achilles tendon (3) 5-6 per cent of its substance is dissolved, a part of which is shown also to be procollagen. The tail collagen of young animals, as well as the collagen of the Achilles tendon, contains 15-20 per cent procollagen in addition to its mucoid component. Besides the mucoid released by heat contraction the procollagen also must be split off in order to obtain a material which is similar to elastin. The metacollagen which remains after extraction of mucoid and procollagen from native collagen is the material which can be regarded as the substance most similar to elastin.

## DISCUSSION

In our opinion the metacollagen fiber cannot be considered equivalent to the elastic fiber found in tissue. The native elastin fiber differs from the collagen fiber in its mucoid components. While the collagen fiber is surrounded by a mucoid sheath containing chondroitin sulphate, which inhibits its dissolution with elastase (3), the elastin fiber is enclosed by a mucoid differing chemically from the abovementioned collagen mucoid. Besides the so-called sheath mucoid, both fibers contain a further mucopolysaccharide, which is less soluble than the sheath mucoid. The sheath mucoid of collagen fiber can be hydrolyzed by the enzyme hyaluronidase, but the insoluble mucoid cannot. The sheath mucoid of elastin can be broken down by the enzyme called elastomucase. Hall (14) was the first who suggested that the elastase is complex in nature and that one of its components is mucolytic, acting on the alkali-labile mucoprotein of elastin. We have already reported (9) that with our very sensitive collagen reaction (the chemical contraction-relaxation) the effect of elastomucase can also be demonstrated on native collagen fiber. The mucoprotein component of metacollagen seems to be similar to the elastomucin of purified elastin. According to our experiments the collagen fibrils are arranged parallel to the long axis and mucoid holds polypeptide chains together. This linkage between mucoid and polypetide is hydrolyzed by the elastomucase.

The elastomucase has no effect upon the sheath mucoid of collagen, but it dissolves both mucoproteins of elastin. According to this collagen can be hydrolyzed by elastase containing elastomucase only if the sheath mucoid and procollagen have been previously dissolved, that is, if metacollagen has been produced. In accordance with this the chemical structure of elastin and collagen in our still incomplete opinion would be as shown in table 1.

The polypeptide chain both of elastin and collagen is of such construction that a soluble component can be separated from both. The presence of a soluble protein component with low molecular weight in elastin isolated by Partridge, Davies and Adair (26) shows a good analogy to procollagen regarding its solubility. According to these authors a polypeptide component is liberated from elastin during short hydrolysis. This product could be called proelastin in analogy with procollagen, which is split off from collagen during short heat treatment. How the proelastin and procollagen are related to each other chemically and physicochemically remains to be proved by further experiments.

TABLE 1. COMPOSITION OF COLLAGEN, METACOLLAGEN, AND ELASTIN AND THE EFFECT OF ELASTASE.

| Fibers | Composition | Elastase Proteolysis | Elasto-mucase Hydrolysis | Elastolysis or Collagenolysis |
|---|---|---|---|---|
| Elastin | Polypeptide chain: (Elastin + proelastin) | + | − | + |
| | Elastomucin$_1$ | − | + | |
| | Elastomucin$_2$ | − | + | |
| Collagen | Polypeptide chain: (Procollagen + Metacollagen) | + | − | − |
| | Chondromucin | − | − | |
| | Elastomucin$_2$ | − | + | |
| Metacollagen | Polypeptide chain: | + | − | + |
| | Elastomucin$_2$ | − | + | |

The results of the work of Partridge, Davies and Adair (26) led them to the view that the substance of purified elastin is a chemically homogenous protein, although it may exhibit heterogeneity of structure at macromolecular level. In their opinion the physical properties of elastic tissue are the result of the macromolecular structure comprising the elementary elastic fibers cemented by collagenous structure and mucoproteins.

Partridge and Davis (25) proved that elastase, besides its mucolytic component, also contains a proteolytic one, and one of its effects upon elastin is the hydrolysis of peptide chains. For this reason we exhibited in table 1 these two effects of elastase, one of which is manifested by the breaking down of polypeptide chains (proteolysis), and the other by the splitting of mucoid. The entire dissolution of elastin and collagen tissue is shown in elastolysis or collagenolysis.

The results of our experiments led to the conclusion that the physiologic and functional entity of collagen fiber involves components which are also to be found in elastin. On the other hand the functional entity of elastin fiber cannot be imagined without some components of collagen fiber. Collagen is chemically linked to the functioning elastin fiber, which has a great physiologic significance. The large quantity of water bound by the polar groups of collagen renders elastin capable of function, that is, makes it elastic.

## SUMMARY

1. The metacollagen prepared from tail tendon collagen of young rats is the substance which is similar to elastin. The metacollagen fiber differs from native collagen in the lack of two components, a mucoprotein fraction and the procollagen. The metacollagen can be prepared from native collagen fiber with three methods: 1) hydrothermal relaxation, 2) chemical relaxation, and 3) extraction.

2. Metacollagen is similar to elastin in the following properties: 1) It shows elasticity in water; 2) Its birefringence increases in lipoid solvents; 3) It can be digested by elastase; 4) The positive birefringence of metacollagen in phenol cannot be reversed to a negative one; 5) The electron microscopic pattern of metacollagen is similar to that of elastin; 6) It does not show acid swelling in dilute organic acids; 7) It can be stained with Weigerts' resorcinfuchsin.

3. Metacollagen, although similar, is not identical with the elastic fiber. According to our still incomplete knowledge it differs from elastin in that it has a different mucoprotein component. Both elastic and collagen fiber contain two mucoproteins or mucopolysaccharide components. One of these is called sheath mucoid. Collagen and elastin fibers have different sheath mucoids. The sheath mucoid of collagen contains chondroitin sulphate which is hydrolyzed by hyaluronidase. In contrast to this the sheath mucoid of elastin is digested by elastomucase. Metacollagen does not contain sheath mucoid, only a mucoid, which is hydrolyzed by elastomucase. Therefore it differs from native elastin fiber as well as from native collagen fiber.

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# BASEMENT MEMBRANES, GROUND SUBSTANCE, AND LYMPHOCYTIC AGGREGATES IN AGING ORGANS*

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Observations in histopathology naturally depend upon techniques that render tissue components visible and suitable for analysis. In the case of the connective tissue matrix or ground substance, formerly called cement substance or connective tissue mucin, it has been chiefly since Gersh and Catchpole (16) in 1949 applied the Hotchkiss-McManus periodic acid leukofuchsin (Schiff) technique, often termed the PAS method, to connective tissue investigations that pathologists have found it easy to examine normal and abnormal intercellular stromal substances. It is the purpose of this communication to review observations made during the past 5 years in studying certain alterations of aging tissue, in the light of the present knowledge of a comparatively young and confused field.

Forty years ago, an amorphous connective tissue matrix was recognized (34, 57). It was seemingly related to mucin and generally was stained with silver nitrate, perhaps because of its higher chloride content (57). Twenty years ago, Maximow and Bloom (35) stated that the amorphous ground substance was difficult to demonstrate and occurred in heavily stained dried preparations of loose connective tissues as a thin, pale film between the fibers. Klemperer (23) has reviewed historically the various histologic theories of intercellular connective tissue substances and their nature.

Gersh and Catchpole (16) considered ground substance and basement membranes to be composed of a polymerized, presumably organized fluid or gel containing oriented fibrillae. The gel and fibrils were regarded as secretory products synthesized by fibroblasts with degrees of glycoprotein polymerization influenced by activity, disease, and age, chiefly mediated through depolymerizing enzymes. Of course, similar substances are also locally secreted by mesenchyme, such as synovial fluid, or by epithelium, such as gastric mucin, or in saliva and urine (6).

Chemically mucopolysaccharides were defined by Meyer (37) as polysaccharides with a hexosamine component. Among many such important substances, including heparin, pituitary gonadotropic hormones, and blood group substances, Meyer considered that the mucopolysaccharide-protein complexes containing a polysaccharide increment of hyaluronic acid formed gels serving to cement cells together, to protect internal surfaces, and to regulate exchanges of metabolites and water by their viscous properties (38). Later, Meyer and Rapport (39) isolated three chrondroitin sulfates, A, B, and C, differing in optical rotations and in susceptibility to enzymatic hydrolysis with hyaluronidases. They thought these substances in basement membranes might function as cationic exchange resins. Mucoproteins have a poorly understood loose association between the polysaccharide and protein. Steps in their intermediate synthesis are now partly worked out. Radioactive sulfur ($S^{35}$) was found to be localized preferentially in the basement membranes of animals, among other sites including the cytoplasm of stimulated fibroblasts (7), with a complete turnover after only two days in basement membranes (2).

Histologically, all basement membranes contain networks of argyrophilic fibers (20). If reticulin is regarded as a related material or precusor to collagen fibril formation, with a relatively larger proportion of amorphous mucoprotein matrix and a membranous nature, rather than the oriented rope-like arrangement of collagen fibril bundles, likely functional adaptive differences between ground substance and collagen are more easily appreciated (25). Successful synthesis of collagen fibrils in vitro

Submitted for publication March 29, 1956.

* Aided by a grant from the American Heart Association to Massachusetts Memorial Hospitals and supported in part by the contract between the Atomic Energy Commission and the New England Deaconess Hospital, contract AT (30-1)-901.

Presented in part at the Histochemical Society Meeting, April, 1954, and before the American Society for Experimental Pathology, April, 1955.

Appreciation is expressed to Drs. John P. Ayer, Philip M. LeCompte, G. Kenneth Mallory, and Shields Warren for advice in the preparation of the manuscript.

from soluble components occurs in the presence of mucoprotein (19).

Histochemically, mucopolysaccharides are mostly acid-reacting with aniline dyes, except for vitreous humor, Wharton's jelly, synovial fluid, and ovarian follicular fluid, which are neutral (8). Mild oxidation as with periodic acid releases aldehyde groups that give positive Schiff staining (9). Other new stains for basement membranes have been developed by Lillie, the allochrome method (31); Ritter and Oleson (47); McManus and Mowry (33); and Kramer and Windrum (26). The last two techniques involve sulfation with strong sulfuric acid and subsequent staining with hematoxylin, azur, or other materials. A very strong coloration of ground substance results.

Alteration of normal ground substance staining in vitro is achieved particularly by the enzyme hyaluronidase (3, 11). Proteolyzing enzymes or a masking of stainability such as occurs with histone also adversely affect the staining reactions (3).

Embryologically, in man the ground substance is particularly abundant in the umbilical cord matrix and is found in embryonic animal brain during the last quarter of gestation. It may serve to orient fibers in the developing brain (18). Congenital abnormalities with particular relationships to ground substance seem likely to include Marfan's syndrome, possible osteogenesis imperfecta, and epidermolysis bullosa congenita. Marfan's syndrome with aortic medial cystic and myxomatous degeneration, cardiac valvular myxomatous alterations, and lax joints may be hormonally induced, as an unusual abundance of pituitary acidophils is apparently characteristic of this syndrome (50).

In the body numerous chemical, pharmacologic, enzymatic, and hormonal substances alter the permeability, inferred polymerization, and stability of ground substance and basement membranes.

Lack of calcium in perfusates leads to softening and dissolution of interendothelial cell cement, and increased acidity also accelerates cement substance dissipation. Excess calcium increases the cement stickiness (10), and drugs like morphine and salicylic acid likewise render the ground substance less permeable (11). Ascorbic acid deficiency in experimental scurvy results in the development of an excess of metachromatic acid mucopolysaccharides, particularly in blood vessel walls, and a deficiency of alkaline phosphatase and fibril formation beyond the reticulin stage (4, 43). Depolymerized ground substance glycoprotein components appear in increased amounts in scorbutic serum (44).

Hormones may either decrease or increase ground substance permeability. Crude extracts of anterior pituitary gland or adrenal cortex lessen the permeability. Cortisone acts to maintain the integrity of capillary cement substance despite the presence of hyaluronidase (36) or altered pressure (27). Pituitary growth hormone experimentally antagonizes cortisone in this respect (27, 58). In chemical inflammation, antiphlogistic cortisone interferes with collagen fibril formation and leads to excess accumulations of mucopolysaccharides (48). Cortisone effects are reflected also in some of the well-known connective tissue changes of Cushing's syndrome. Myxedema is characterized by marked local accumulations of mucopolysaccharide, particularly rich in hyaluronate, in the connective tissues (56) accompanied by lessened permeability (11). Thyroidectomy in man has been followed by mucopolysaccharide accumulations, so-called chromatropic degeneration, in the aortic media (24).

Hyaluronidase, pituitary gonadotropic hormones and possibly estrogens all operate to exaggerate ground substance permeability, according to Duran-Reynals (11). Parathyroid hormone produces a depolymerization and solution of the ground substance, chiefly in bone and epiphyseal cartilage (14). Many different diseases are accompanied by dissolution or alleged depolymerization of ground substance and other mucoproteins. For example, virsuses of influenza type have this activity (5), and atopic dermatitis may be accompanied by an exaggerated mucoprotein breakdown (46).

The rheumatic diseases (6), including also serous inflammations with fibrinoid or hyaline degeneration (1), lipoid nephrosis (22), toxemia of pregnancy (45), thrombocytopenic hemorrhage (15), and experimental endocarditis (32) without or with arthritis (21), have in common the pathogenetic sequence of ground substance swelling with depolymerization and resulting increases of circulating mucoprotein. "Collagen diseases" including disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis, scleroderma, and also scleredema (54) share in this pathogenesis, and much evidence at hand would favor considering them

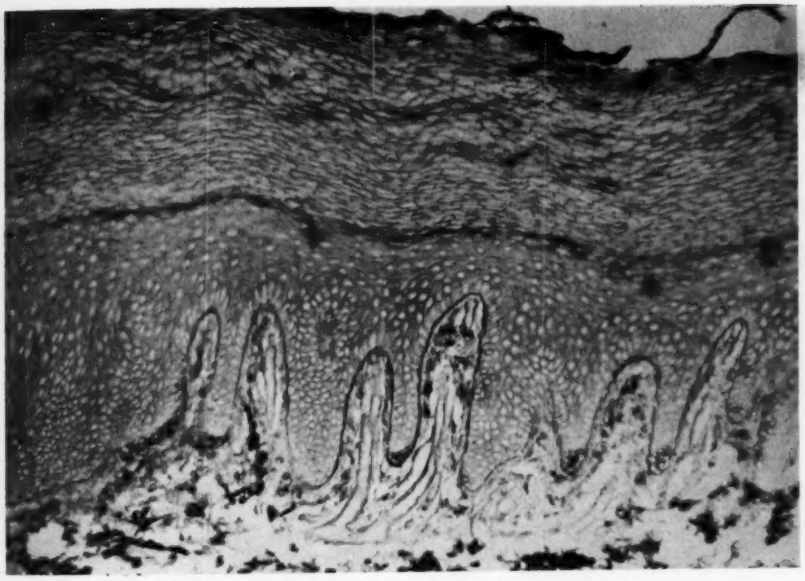

Fig. 1. Skin from sole of the foot, stained by McManus-Mowry method, with the thickened basement membrane shown as an irregular black line beneath the epidermal basal cells, X125.

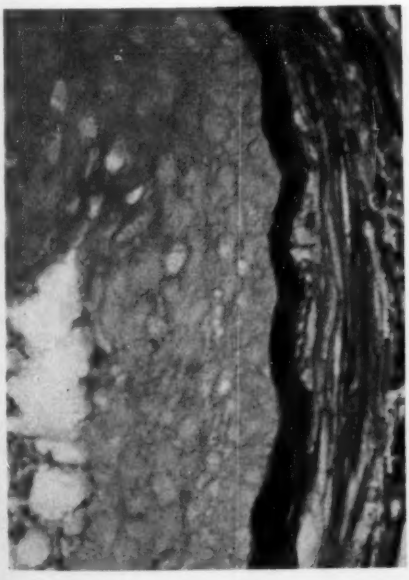

Fig. 2. An epidermal inclusion cyst with dark thick basement membrane, X500.

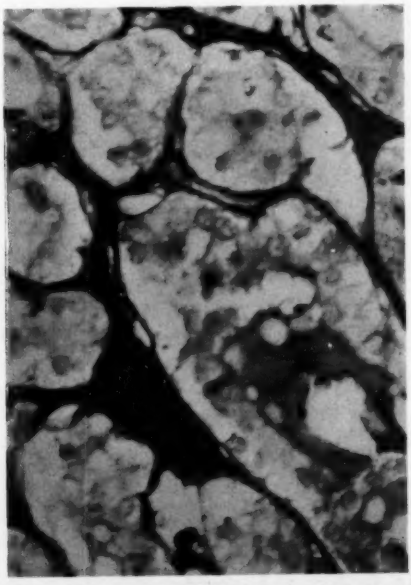

Fig. 3. Thickened thyroid basement membranes in a follicular adenoma. McManus-Mowry stain, X500.

Fig. 4. Bronchial asthma, with the very dark-stained thickened bronchial basement membrane typical of this condition, X150.

Fig. 5. Irregularly thickened ileal basement membranes in edematous intestine with regional ileitis, X250.

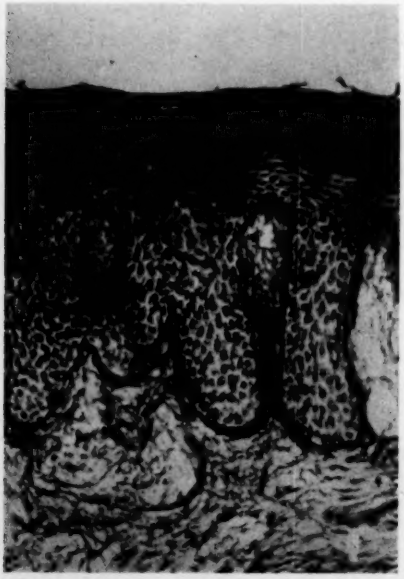

Fig. 6. Skin with neurodermatitis, demonstrating thickened basement membrane stained by the Foot silver method, X150.

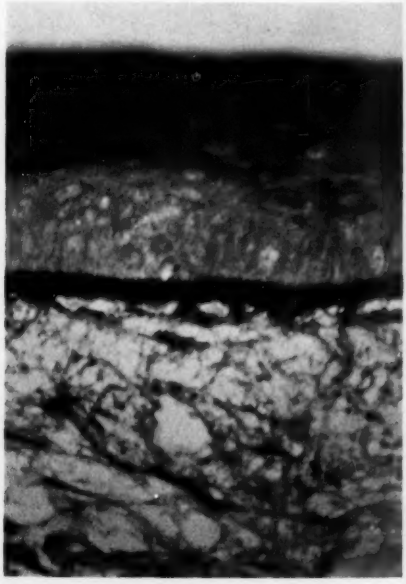

Fig 7. Thickened serrated basement membrane in a laryngeal polyp. McManus-Mowry stain, X500.

to be at least in part ground substance diseases. Glomerulonephritis today is regarded as an antigen-antibody reaction directed particularly against glomerular basement membranes, and is characterized morphologically by local mucoprotein degeneration (13).

Diabetes mellitus, a disease of glucose, glycogen, and mucoprotein metabolism, has important ground substance abnormalities, particularly evident in the vascular complications (29). A qualitatively abnormal mucopolysaccharide substance is deposited particularly in the walls of the glomerular and retinal capillaries, which carry normal relatively high pressures. This material is abnormal in both its histochemical and ultra-violet absorptive properties, while the mucopolysaccharides that collect in atherosclerotic degeneration or glomerular atrophy appear qualitively normal by these criteria (51, 55).

Which of these physical, chemical, and hormonal influences are most significant in tissues of aging persons, in relation to alterations of ground substance? In the following paragraphs, some observations made on aging human tissues are considered.

Pressure is one significant factor. Pressure zones of the body, such as the sole of the foot, normally show an increased subepithelial condensation of the ground substance and reticulum in the form of a thicker basement or corium membrane than occurs in skin elsewhere. Just as frictional forces produce a hyperkeratotic outermost calloused surface, they likewise lead to development of a thickened basement membrane cementing layer beneath the epidermal basal cells (fig. 1). The transient skin marks produced by pillows, clothing, or pressures of pack straps, rifles, etc., partly reflect the plasticity of ground substance gel in the dermis. As Willis (59) has pointed out, the mechanical forces involved include stretch against an elastic recoil.

Situations of chronically increased localized pressures in tissues, such as accompany expanding spherical tumors, including epidermal inclusion cysts, fibroadenomas of breast, or adenomas of thyroid are likewise characterized by unusual thickenings of basement membrane structures at boundaries between the epithelium and stroma both within and at the margins of the tumors (fig. 2, 3). Conditions of chronic edema with or without spastic overactivity of adjacent smooth muscle, such as affect the bronchi in asthma, the intestine in regional ileitis, dermatitides like psoriasis and neurodermatitis, and edematous polyps of choanae and larynx have in common a thickening of the basement membranes (fig. 4-7). Whether the lesions are of mechanical origin like the laryngeal polyp, allergic etiology as in nasal polyps and bronchial asthma, or of neoplastic or unknown basis, excessive and prolonged compression exaggerates the condensation and localization of excess ground substance components against the epithelial tissue boundaries.

Study of kidney biopsies from hypertensive patients, histologically and histochemically, suggests that similar ground substance condensation occurs in the arteriolar subendothelium (53). Judging from transitional examples the development of renal arteriolar sclerosis passes through stages of vascular muscular spasm, edema, fibroblastic proliferation at the expense of muscle cells, and localized pooled collections of strongly PAS positive ground substance in the partly degenerated vessel walls. Later hyaline alteration of the collagen supervenes more or less uniformly. The exaggerated accelerated ground substance accumulation and subsequent connective tissue aging of small arterial vessels in hypertension have histochemically the same pathogenetic sequences as occur in stroma at the margins of expanding spherical tumors, with the important difference that arteriolar sclerosis is characteristically focal, perhaps reflecting greater local differences in mechanical forces.

Atrophy of parenchyma, as exemplified in the aging kidney, is conversely accompanied by a blurring, thinning, focal fibrillation and disappearance of some basement membranes of the renal tubules and Bowman's capsules. In the kidney and elsewhere a diminished blood supply secondary to vascular narrowings, or withdrawal of hormonal stimulation from certain target organs like prostate and breast, or decreased nutrition or metabolic activities are the basic factors in parenchymal atrophy. Here the basement membrane dissolutions appear both secondary and passive, perhaps associated merely with tissue shrinkages of diverse causation. It may be pertinent that age is accompanied by an increased level of serum mucoprotein (28).

When basement membranes dissolve locally in the kidney, the adrenal cortex or medulla, the portal regions of liver, or in focal atrophy

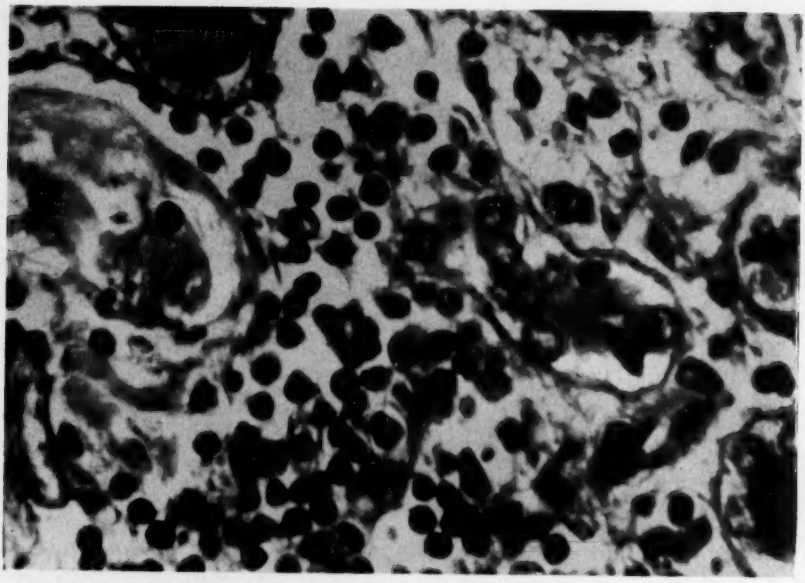

Fig. 8. Kidney tubules locally atrophic and devoid of basement membranes, associated with accumulation of lymphocytes. Pearse PAS stain, X850.

Fig. 9. Adrenal cortical focus of atrophy with basement membrane dissolution and lymphocytic aggregate, X850.

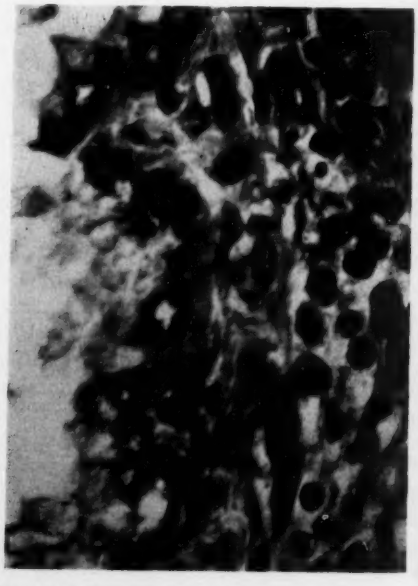

Fig. 10 Degeneration of prostatic acinus, with atrophy and lymphocytic infiltrate, X850.

of prostate acini, thyroid follicles and breast ducts, aggregates of lymphocytes commonly collect. These lymphocytic collections in older persons' tissues characteristically are adjacent to viable cells devoid of their customary basement membrane sheaths. Nodules of lymphocytes without germinal centers, and containing occasional macrophages, are rather a commonplace in various aging parenchymal tissues (fig. 8-10).

Conventionally these lymphocytic aggregates are considered as indications of inflammation. However, as Opie (42) has recently pointed out, "the word inflammation loses all significance when it is defined in terms which include all pathologic change save neoplasm." In the absence of necrosis, visible parenchymal degeneration, or exudation of polymorphonuclear, eosinophilic leukocytes, or particularly plasma cells, traditional diagnoses of chronic inflammation would seem to hinder a better understanding of the basic mechanisms involved, when applied to the focal homogeneous aggregates of lymphocytes so common in the aging kidney, liver, adrenal and thyroid glands, prostate, and breast.

A hint as to a possible leukotactic force attracting lymphocytes is provided by the normal embryology of thymus. At first composed of intact epithelium, it lacks lymphocytes until the layers of epithelium break up into the unique epithelial reticulum and in part form Hassall's corpuscles. At this time lymphocytes infiltrate the thymus and remain thereafter as a major component. PAS and McManus-Mowry stains for basement membranes show the Hassall's bodies to be devoid of any mucoprotein sheaths.

It seems that proteins, either autologous or heterologous, probably attract lymphocytes. Murphy (41) has discussed the accumulation of lymphocytes experimentally around heterologous tissue grafts, and Sabin and associates (49) described some similar effect of tuberculoprotein. Ehrich (12) concluded that while the functional significance of lymphocytes is not yet clear, they are instrumental in the destruction of toxic products of protein metabolism and deliver components for protein production.

When unaccompanied by plasma cells the lymphocytic aggregates around unprotected kidney tubules, bile ducts, thyroid follicles, prostatic acini, or breast ducts that have undergone local atrophy and basement membrane dissolution do not fit easily into modern concepts of inflammation, involving antigen destruction and antibody formation. Less conclusively, degenerative dissolution of basement membranes in various skin diseases, in early epidermoid carcinomas, and in neoplasms such as testicular embryonal carcinomas or ovarian dysgerminomas, may serve to attract lymphocytes simply because of the exposure of cell proteins locally unshielded by mucoprotein ground substance. The most likely function that lymphocytic foci may serve here is to act upon and alter chemically the soluble autologous proteins that leak from unprotected cells, in a way analogous to lymphocytic effects upon the mild irritants or toxic materials in lymph passing through lymph nodes (34).

In what way lymphoctyes function to replace or serve to compensate for the loss of basement membranes is unknown. The recognized lymphatic tissue functions as sources of macrophages and plasma cells are not actively invoked. The presence of lymphocytic nodules without evident ground substance alterations in actively growing tissues like bone marrow, intestinal epithelium, and endometrium might indicate that sometimes lymphocytes can form a local source of ready-formed nucleoprotein, but this possibility does not apply equally to aging organs. Incidentally, gonadal tissues grow actively without the appearance of any lymphocytic nodules, perhaps because of the genetic necessity of maintaining the purity of the germinal cell nucleoprotein unadulterated by any nucleoprotein contribution from somatic cells.

Diseases of older persons characterized by excessive tissue accumulations purely of lymphocytes, unaccompanied by other exudation or evidences of inflammation, occur chiefly in the thyroid, salivary glands, and skin. Hashimoto's struma and Mikulicz's disease are marked by lymphocytic infiltrates and the formation of lymphatic nodules with germinal centers. By these criteria these two diseases are distinguished from chronic nonspecific thyroiditis and sialadenitis, which are ordinary chronic inflammations with numerous plasma cells present.

Studies of the basement membranes in Hashimoto's and Mikulicz's diseases have shown dissolutions of basement membranes to characterize them and possibly to antedate the lymphocytic infiltrations (52). Thyroid, salivary gland, and thymus are all branchial derivatives,

and embryologic relations may in part explain their common tendency to localize pure lymphocytic infiltrates. Also, more thyroid hormone passes through the follicular basement membranes of the thyroid gland than through any ground substance elsewhere. Local hormonal effects might tend to soften and dissolve the components. Since insufficient thyroid hormone leads to myxedema with an excessive ground substance deposition, prolonged exposure either to normal or heightened hormonal concentrations might conversely contribute to abnormal local deficiency of the basement membrane mucoprotein. Secreted thyroid cell mucinase is normally a factor in thyroglobulin resorption. Excessive mucinase activity may explain the lymphatic tissue collections termed "strumitis" commonly seen with primary thyroid hyperplasia (17). Hyperthyroidism is not *per se* considered to be a common precursor of genuine Hashimoto's struma.

Hormonal and enzymatic influences on local metabolism, particularly ascribable to the thyroid, its mucinase and other proteolysins, are thus considered important, like pressure, in ground substance maintenance in the aged. At present the relative importance of various other specific endocrine secretions and enzymes is not clear.

Skin is relatively rich in connective tissues, and lymphocytes predominate in the cellular infiltrates of many so-called inflammatory dermatoses (40). Pure lymphocytic aggregates with myxoid ground substance degeneration occur chiefly in pellagra and lichen sclerosus et atrophicus. Fibrinoid necrosis and lymphocytic collections are found together in the dermatologic manifestations of rheumatic fever, rheumatoid arthritis, and also in granuloma annulare, and discoid or disseminated lupus erythematosus (30). In exfoliative dermatitis the most extreme degeneration of basement membranes and ground substance is observed, with lymphocytes characterizing the dermal reaction.

If one views skin manifestations of pellagra, rheumatic fever, and lupus erythematosus as essentially enzymatic lesions possibly involving coenzymes I and II, streptolysin, and a proteolysin like "L.E. factor," respectively, the importance of enzymatic mechanisms in ground substance maintenance is again evident. Age alone does not seem to be associated with any alteration of these enzymes.

It is appreciated that much of the foregoing discussion may be thought to be out of date, speculative and rightly belonging to the general descriptive pathology of the nineteenth century. Observations of tissue changes microscopically and attempts at their interpretation remain valid scientific methods, although somewhat unfashionable in medical research today. Bearing in mind that ground substance and basement membranes were to pathologists largely invisible and theoretic until about 10 years ago, perhaps a hiatus in the understanding of some simple but rather important morphologic changes in connective tissue mucoproteins may be excused. Quantitative and analytic studies of ground substance are to be anticipated in increasing numbers, with consequent improvement in our knowledge of its metabolism and diseases.

## SUMMARY

Based on observations with newer stains of ground substance and basement membranes, supported in part by histochemistry and ultraviolet microscopy, various present ideas of the composition of connective tissue mucoprotein and some of its reactions to physical and chemical stimuli have been reviewed. Pressure and stretch tend to condense ground substance mucoprotein against epithelial and other barriers. Endocrine and enzymatic factors may cause ground substance degeneration. Analogies in normal thymic embryology and various diseases are thought to support the importance of ground substance sheaths as protecting layers normally preventing parenchymal cell proteins from exposure to the internal environment and the consequent attraction of lymphocytic aggregates. Parenchymal atrophy is sometimes preceded and accompanied by localized basement membrane dissolutions, with accumulations of lymphocytes in aging organs.

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# TREATMENT OF SENESCENT MALE RATS WITH CORTISONE ACETATE ALONE OR TOGETHER WITH SEX AND THYROID HORMONES

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In the present experiments the effects of comparatively small, non-toxic doses of cortisone alone, or in combination with testosterone and estradiol compounds and desiccated thyroid, were investigated.

An extensive literature refers to the effects of cortisone on various organs, tissues, and functions, and it was reviewed in several publications (2, 6, 7, 11, 16, 17, 18, 19, 21).

While changes in the weight and histologic structure of the adrenals and lymphoid organs were investigated in most cases, those in other organs were examined less frequently (1, 2, 8, 12, 13, 24). Moreover, since large doses of cortisone are used for therapeutic purposes, chiefly the effects of these doses were investigated. Large doses, however, possess toxic properties (2, 7, 21, 26, 27) which prevent the investigation of physiologic effects.

Thus, large doses of cortisone compounds produced atrophic changes in the adrenals, thymus, spleen, and lymph nodes (1, 11, 24). For example, in the experiments of Antopol (1) the respective weights of the adrenals, thymus, and spleen were 2.34, 48.1, and 164 mg. in control mice, while in the cortisone treated animals they were 1.56, 8.05, and 51 mg., respectively. In the adrenals a decreased size of cortical cells, depletion of lipoid granules, and occasional development of small adenomas were observed. The adrenal atrophy is explained at least partly by a compensatory suppression of the cortex, produced by administration of excessive amounts of the adrenal hormone.

In the spleen, besides atrophy and destruction of cells, Teilum and associates (23) recorded a hyalinosis of the splenic reticulum in perifollicular and perivascular zones and a decrease in number of plasma cells.

The weight and structure of the kidneys were usually not changed (24, 25), but in some cases a thrombosis of glomerular capillaries and granulomatous nests were found (2).

In the thyroid a flattening of the epithelium and increased amount of hard colloid were observed, while the foci of interstitial inflammation or necrosis were found in the pancreas (2). However, in other experiments (8, 24, 25) no changes were recorded in these organs.

Contradictory observations were also reported on the changes in cardiac and skeletal muscles. While in some experiments (2, 13) degenerative lesions and even nests of necrosis were observed, in other investigations (8, 12, 24, 25) a normal weight and structure of the heart were found.

The testes, seminal vesicles, and prostate in male mice and the ovaries in females appeared smaller in Antopol's experiments (1), but by other authors (23) the male sex organs were found to be normal.

In guinea pigs Harris and associates (8) did not notice any significant changes in the weight of the thymus, spleen, heart, pancreas, and lungs, but they found a greatly increased weight of the liver (from 50 to 123 per cent) and a less pronounced increase of the kidneys (from 8 to 20 per cent) and testes (up to 33 per cent). These authors observed the same effect on the liver of rabbits, but not in mice, rats, or chicks. Histologically hepatic cells of guinea pigs were enlarged. Chemical investigation showed an increased nitrogen, water, and glycogen content in the liver of guinea pigs. Glycogen accumulation in the liver cells after cortisone injections was also observed in mice, rats, and rabbits (2, 20, 23).

The above mentioned changes were also produced by ACTH administration. Therefore, according to these results the hypertrophy of the liver produced by cortisone or ACTH should be explained by protein and glycogen deposition and by water retention. In contrast to this, Winter and associates (24) found no changes in the fat, nitrogen, and phosphorus content of the liver and kidneys of cortisone injected rats.

Various lymphoid tumors, rhabdomyosarcomas, ependymyomas, and malignant leukemia were temporarily inhibited or regressed by cortisone compounds in experimental animals (3, 4, 9, 10, 11, 22, 27, 28), but Antopol and asso-

Submitted for publication September 15, 1955.

ciates (1, 2) observed a development of adenomas in the adrenal cortex of cortisone injected mice. Cade (5) reviewed the literature on the subject and reported his own results on the effects of double adrenalectomy on breast cancer in women. Their life after the operation was maintained by cortisone injections. In about 60 per cent of Cade's cases a subjective and objective improvement was obtained.

## MATERIALS AND METHODS

Two experiments were performed on a total of 68 male normal rats.

The arrangement of the groups in both experiments was the same, the difference being only in the dosage of hormones administered. The changes in the weight or organs were similar in both experiments, being somewhat more pronounced in the Experiment II with larger doses. For economy of space the tables of relative weights of organs and those of measurements of cells and nuclei in the kidneys and adrenals were omitted. These data are, however, discussed in the text. The number of rats in each group of experiments is recorded in tables 1 and 2. Control animals were untreated littermates of rats in experimental groups.

Relative weights of organs were calculated per 200 Gm. of fat-free body weight, the total body fat being calculated by the formula used in previous experiments (14).

The histologic technique and the paper replica method used for the measurement of cells and nuclei were the same as in previous experiments (14, 15).

The statistical method and designations used were also the same as in previous investigations.*

*Experiment I* was performed on 34 rats, 6 of which served as controls. The duration of the experiment and of hormonal treatment was 67 days. The average age of animals at the end of the experiment was about 31.5 months. Cortisone acetate was injected subcutaneously in crystals suspended in 5 per cent gum acacia solution, in the dose of 0.3 mg. twice a week. Testosterone propionate was implanted subcutaneously in 20 mg. pellets containing 5 mg. of the hormone + 15 mg. cholesterol. The absorption from these pellets was very small, about 0.22 mg. per week. Desiccated thyroid was given orally by pipette 25 mg. twice a week during the first 53 days and once a week during the last two weeks. Two subcutaneous injections of 0.022 mg. of estradiol-3-benzoate-n-butyrate (estradiol B.B.) were given only during the first week of the experiment.

*Experiment II* was performed on 34 rats, 9 of which served as controls. The duration of the experiment was 45 days. The average age of rats was about 21 months. Cortisone acetate was injected subcutaneously in crystals suspended in 5 per cent gum acacia solution, 1.5 mg. once a week during first 30 days of the experiment, and 2 mg. once a week during the remaining period. Testosterone dipropionate was also injected in crystals in the gum acacia solution, 0.5 mg. every tenth day during the first half of the experiment and every fourteenth day during the remaining period. Desiccated thyroid was given by mouth, at first 20 mg. once a week and during the last 4 weeks of the experiment 8 mg. once a week. Two injections of 0.03 mg. of estradiol B.B. were given subcutaneously during the first week only.*

## RESULTS

As compared with Experiment I, in Experiment II the doses of cortisone acetate and especially of testosterone compound were considerably larger; those of estradiol B.B. were slightly larger, while those of desiccated thyroid were smaller Accordingly, the effects of cortisone acetate and especially of testosterone compound were more pronounced in Experiment II.

*Testes.*—As in a previous study (14) a 4 stage system was used for rating testicular degenerative changes. In present experiments the aging degenerative changes in control untreated rats were more pronounced than in the previous investigation (14, 15). Thus, Stage 1 changes were present in all control rats; Stage 2 or 3 changes were observed as well in about 25 per cent. Even the extreme Stage 4 of degeneration was observed in a few seminiferous tubules of some control rats in Experiment I on older rats.

Cortisone had no significant effect on the weight or histologic structure of the testes.

A larger dose of testosterone compound (Experiment II), administered alone or together with other hormones, had the usual atrophying effect on these organs. This effect was shown both by a decreased weight of the testes (table

* Statistical evaluation of the results obtained was performed by C. W. Shaddick, the statistician of the Health Department of the London County Council.

* The hormones used were supplied by Ciba Ltd., by courtesy of Dr. K. Miescher.

TABLE 1. EFFECT OF HORMONES ON ACTUAL WEIGHTS OF ORGANS IN EXPERIMENT I.

| Organs | Controls | Testosterone Propionate | Cortisone Acetate | | |
|---|---|---|---|---|---|
| | | | Alone | + Testosterone Propionate | + Testosterone Propionate + Estradiol B.B. + Desiccated Thyroid |
| Testes (Gm.) | 0.90 | 0.98 | 1.15 | 0.77 | 0.92 |
| Seminal vesicles (Gm.) | 0.85 | 0.84 | 0.76 | 0.84 | 0.74 |
| Prostate (Gm.) | 1.30 | 1.56 | 1.52 | 1.37 | 1.58 |
| Penis (mg.) | 355 | 381 | 344 | 370 | 367 |
| Preputial glands (mg.) | 185 | 229 | 241 | 234 | 259 |
| Adrenals (mg.) | 57.8 | 65.2 | 51.4 | 57.2 | 61.6 |
| Thyroid (mg.) | 31.0 | 34.7 | 30.3 | 32.9 | 31.2 |
| Hypophysis (mg.) | 16.0 | 22.0 | 15.3 | 17.0 | 20.1 |
| Liver (Gm.) | 12.03 | 12.55 | 12.76 | 12.15 | 13.22 |
| Kidneys (Gm.) | 2.45 | 2.82 | 2.75 | 2.56 | 2.76 |
| Spleen (mg.) | 910 | 923 | 975 | 1006 | 1002 |
| Heart (mg.) | 1209 | 1360 | 1298 | 1263 | 1395 |
| Brain (Gm.) | 2.10 | 2.07 | 2.12 | 2.06 | 2.06 |
| Sex fat + retroperitoneal fat (Gm.) | 33.5 | 26.4 | 32.5 | 27.5 | 23.0 |
| Final body weight (Gm.) | 410 | 386 | 409 | 396 | 361 |
| Number of rats in each group | 6 | 7 | 7 | 8 | 6 |

TABLE 2. EFFECT OF HORMONES ON ACTUAL WEIGHTS OF ORGANS IN EXPERIMENT II.

| Organs | Controls | Testosterone Dipropionate | Cortisone Acetate | | |
|---|---|---|---|---|---|
| | | | Alone | + Testosterone Dipropionate | + Testosterone Dipropionate + Estradiol B.B. + Desiccated Thyroid |
| Testes (Gm.) | 2.82 | 1.36 | 2.92 | 1.34 | 1.38 |
| Seminal vesicles (Gm.) | 0.69 | 1.27 | 0.87 | 1.07 | 1.11 |
| Prostate (Gm.) | 1.29 | 1.98 | 1.73 | 1.96 | 2.02 |
| Penis (mg.) | 359 | 392 | 370 | 412 | 376 |
| Preputial glands (mg.) | 105 | 163 | 143 | 169 | 137 |
| Adrenals (mg.) | 36.1 | 40.5 | 37.5 | 35.2 | 39.1 |
| Thyroid (mg.) | 21.7 | 23.2 | 24.2 | 25.9 | 24.6 |
| Hypophysis (mg.) | 11.7 | 12.0 | 13.9 | 12.5 | 12.5 |
| Liver (Gm.) | 9.57 | 10.75 | 10.94 | 10.92 | 10.03 |
| Kidneys (Gm.) | 2.19 | 2.52 | 2.52 | 2.47 | 2.59 |
| Spleen (mg.) | 1304 | 1384 | 1299 | 1297 | 1350 |
| Heart (mg.) | 1122 | 1281 | 1297 | 1230 | 1202 |
| Brain (Gm.) | 2.16 | 2.12 | 2.19 | 2.19 | 2.19 |
| Sex fat + retroperitoneal fat (Gm.) | 18.4 | 21.3 | 21.4 | 24.9 | 20.7 |
| Final body weight (Gm.) | 379 | 386 | 389 | 391 | 373 |
| Number of rats in each group | 9 | 6 | 6 | 6 | 7 |

2), and histologically by more pronounced degenerative changes.

*Secondary sex organs.*—While a larger dose of testosterone compound in Experiment II, alone or with other hormones, produced the usual hypertrophying effects on the seminal vesicles, prostate, preputial glands, and penis (table 2), these effects in Experiment I were slight and statistically not significant, except in the case of the prostate in the group of rats to which all hormones used were administered simultaneously ($P < 0.05$). These hypertrophic changes were confirmed by histologic examination.

Unexpectedly cortisone had a similar but weaker effect which was statistically significant only in the case of the prostate with a larger dose of cortisone (table 2, $P < 0.001$). However, in the groups to which testosterone and cortisone compounds were administered simultaneously, no definite cooperative effect of cortisone and testosterone compounds was noticed.

The slight androgenic effect of cortisone might be explained by a weak androgenic property of this hormone or by the presence in the compound used of impurities in the form of other definitely androgenic corticoadrenal hormones (e.g., adrenosterone).

Experiments on castrated rats with cortisone especially carefully purified from corticoadrenal androgens would clarify this point.

*Adrenals.*—Comparatively small and definitely non-toxic doses of cortisone acetate used in the present experiments did not produce any effect on the weight of the adrenals (tables 1 and 2) or size of cortical cells and their nuclei. For example, the average size of fasciculata cells of control rats in Experiments I and II was 10.49 and 10.74 mg., respectively, (as measured by their paper replicas). In "cortisone" groups the respective figures were 11.34 and 10.97 mg.

Since the doses used of testosterone compounds were also small and therefore did not cause atrophy of the corticoadrenal cells (10.58 and 10.08 mg.), the combined administration of both hormones also did not produce any statistically significant atrophying effect in both experiments (11.13 and 12.83 mg., respectively), showing even a slightly larger size of cells. Therefore, the atrophying effect of cortisone recorded by all workers using large doses apparently should be explained by a toxic action of excessive doses.

The only change in the adrenals observed in the present experiments was a partial or, in some cases, a complete depletion of lipoid granules in the zona glomerulosa. This change was found in about 50 per cent of rats treated with cortisone alone, while it occurred in nearly all rats treated with testosterone compounds alone or together with other hormones.

*Liver.*—In previous experiments (15) it was found that androgenic hormones produced definite hepatotrophic effects in castrated rats, but in normal animals the increase in the weight of the liver and hypertrophy of cells were small or absent, while nuclei could become hypertrophic.

In the present experiments, possibly due to more pronounced changes in the testes, in control intact rats the cytoplasm of hepatic cells was as small (8.22 and 8.77 mg., table 3) as observed previously in castrated rats of similar age (8.66 mg., Korenchevsky and associates (14, table 7)) while in normal intact rats it should measure about 11.79 mg. (14).

Possibly this explains why in the present experiments testosterone compounds, producing a small but statistically significent increase ($P < 0.05$ in Experiment I and $P < 0.02$ in Experiment II) in relative weights of the liver, greatly hypertrophied the cytoplasm of hepatic cells (table 3, $P < 0.01 - 0.001$). Nuclei, however, were significantly enlarged only in Experiment II ($P < 0.05$).

Similar changes were observed in the groups in which testosterone compounds had been administered together with other hormones.

Cortisone in both experiments produced only a slight increase, statistically not significant, in the weight of the liver (tables 1 and 2), but about the same hypertrophy of the cytoplasm as did androgens ($P < 0.01 - 0.001$). The size of the nuclei, however, did not change significantly.

Therefore, contrary to the results obtained by Harris and associates (8), not only in guinea pigs and rabbits but in rats as well the hepatotrophic effect of cortisone could be observed. Probably the discrepancy can be explained by different doses used, since Harris and associates recorded the loss in body and liver weights of their rats. This suggests that probably too large and therefore toxic doses of cortisone were employed (unfortunately the dosage was not stated in the paper).

Those pathologic changes which are usually observed in the liver of aging rats, namely small nests of round cell infiltrations and bile duct hyperplasias (14, 15), were present both

TABLE 3. EFFECT OF HORMONES ON LIVER CELLS.

| Groups | Average Weight of Paper Replica (Mg.) | | | | | |
|---|---|---|---|---|---|---|
| | Experiment I | | | Experiment II | | |
| | Cytoplasm | Nucleus | Ratio of Nucleus to Cytoplasm | Cytoplasm | Nucleus | Ratio of Nucleus to Cytoplasm |
| Controls | 8.22 | 1.16 | 0.141 | 8.77 | 1.09 | 0.126 |
| Cortisone acetate | 10.48 | 1.15 | 0.110 | 10.47 | 1.09 | 0.104 |
| Testosterone propionate (Exp. I) or dipropionate (Exp. II) | 11.79 | 1.19 | 0.103 | 10.95 | 1.18 | 0.110 |
| Cortisone acetate + Testosterone propionate (Exp. I) or dipropionate (Exp. II) | 10.68 | 1.23 | 0.116 | 10.66 | 1.17 | 0.110 |
| Cortisone acetate + testosterone propionate (Exp. I) or dipropionate (Exp. II) + estradiol B.B. + desiccated thyroid | 11.22 | 1.39 | 0.105 | 10.55 | 1.12 | 0.106 |

in control and treated rats in about the same number and were of about the same size.

*Kidneys.*—Previously (15) it was found that the renotrophic effect of androgens was very pronounced in castrated rats but usually was weak or absent in normal rats. In the present experiments it was also weak, the renal enlargement being statistically significant only in relative weights ($P < 0.5$ in Experiment I and $<$ 0.02 in the Experiment II). The cells of the convoluted tubules were enlarged only slightly and statistically not significantly (as measured by the paper replica method).

Cortisone in the doses used had an effect similar to that of testosterone compounds. The increase in weight of the kidneys valued about 15 per cent and it was statistically significant only in relative weights ($P < 0.05 - 0.02$). Although the enlargement of the cells in the renal convoluted tubules was statistically not significant, a definite enlargement of their nuclei was observed in Experiment II (1.78 mg. in control rats and 2.19 mg. in cortisone injected animals, $P < 0.05$).

Thus, the results obtained in the present experiments on rats were similar to those on guinea pigs by Harris and associates (8), who, however, did not find these changes in rats.

Combined administration of testosterone and cortisone compounds did not significantly increase the effects produced by each of these hormones separately. When, however, all 4 hormones used were given simultaneously, the renotrophic effects, especially with a larger dose of cortisone acetate, in Experiment II, were more pronounced. This effect was shown by the relative weight of the kidneys (23.6 per cent increase, $P < 0.001$) and the enlargement of renal cells and nuclei (7.67 and 1.78 mg., respectively, in control rats; 8.50 and 2.02 mg., respectively, in treated rats, $P < 0.02$).

*Heart.*—A cardiotrophic effect of androgens on senescent rats was established previously (15).

In the present experiments a stimulating effect of testosterone and cortisone compounds on the heart was similar to that on the liver and kidneys, being slight and more pronounced in Experiment II. It was statistically not significant in actual weights but was significant ($P <$ 0.05) in relative weights when these hormones were administered alone or together or simultaneously with thyroid and estradiol hormones.

The number of enlarged cardiac fibers was not counted in present experiments, but previously (15) it was found that after testosterone administration this value increased in castrated, but not in normal male senescent rats.

*Spleen.*—As previously (14) observed in intact senescent rats, in control animals of the present experiments the number of mitoses and giant cells was also small as compared with

these values in young rats. No difference between control rats and treated animals was noted in actual or relative weights, histologic structure, number of mitoses, and giant cells in the spleen. Therefore, the atrophic changes in this organ after the injection of large doses of cortisone compounds, observed by authors using these doses, should be explained by their toxicity.

*Other organs.*—Winter and associates (24) recorded that, after cortisone injections, the hypophysis and thyroid of normal rats were normal both histologically and by weight.

In the present experiments no statistically significant difference was found in the weight of the hypophysis, thyroid, and brain, nor in the histologic structure of the thyroid and pancreas. The thyroid had a structure of an active gland in rats of all groups. The number of metaplasias, small cysts, and adenomas seemed to be slightly increased in the thyroids of treated animals. The number of rats in the various groups, however, was too small for definite conclusions on adenomagenic effects of hormones.

## SUMMARY

1. In 53 intact male senescent rats the effect of comparatively small non-toxic doses of cortisone acetate administered alone, or together with testosterone compounds, estradiol B.B., and desiccated thyroid was investigated on the weights and histologic structure of various organs. Fifteen animals served as controls.

2. Some effects of cortisone were found to be similar to, but weaker than, those of androgens, being more pronounced with a larger dose of cortisone.

3. In the case of the sex organs, cortisone produced a hypertrophy of the prostate and a similar, but considerably lesser effect on the seminal vesicles, penis, and preputial glands. In contrast to the usual androgenic effect on the testes, the doses used of cortisone did not produce atrophy of these organs.

4. Like androgens, cortisone also produced a definite, but limited stimulating effect on the liver, and a less pronounced stimulation of the kidneys and heart.

5. Since the effects of androgenic hormones are always much more pronounced in castrates than in normal intact animals, it was suggested that "androgenic" properties of cortisone should be also studied on castrates.

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# PERITONEAL FLUID MAST CELLS: THEIR NUMBERS AND MORPHOLOGY IN RATS OF VARIOUS BODY WEIGHTS (AGES)

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The statistical occurrence of mast cells as a function of age has been studied both in man (4, 6, 9) and in the rat (7). Considerable work has been conducted to determine whether mast elements are under hormonal regulation. In this connection, it has been demonstrated (12) that the mast cells within the peritoneal fluid of the rat are affected by hypophysectomy and that the observed changes, namely morphologic abnormalities suggesting cellular damage, are not evident in hypophysectomized rats treated with a growth hormone preparation (11, 13).

In this paper, data obtained for peritoneal fluid of intact rats in the course of several studies have been analyzed with respect to mast cell numbers and morphology as a function of body weight (age).

## MATERIAL AND METHODS

Rats of a modified Long-Evans strain were used. Peritoneal fluid was obtained and studied as previously described (14) and consists, briefly, of performing an abdominal incision followed by careful collection of as much peritoneal fluid as possible with a fine medicine dropper. This fluid is then measured in a special pipette with the aid of an Adams' suction unit. The method yields only minimal values, but errors of sampling seem to remain fairly constant because of an inverse relationship between cellular concentration and volume of fluid obtainable under controlled conditions. All counts were performed on cells within the hemacytometer following dilution of the fluid with Randolph's phloxine-methylene blue in propylene glycol (15).

Body weight was taken as a rough estimate of age because no birth date records were available for the animals. Data were analyzed for male rats only, since female animals were not available over a wide enough range of body weights to justify their inclusion in this study. Inasmuch as the values were obtained from various experiments, all parameters were not studied for every animal. Whenever a statistical value is stated below, the number of animals on which it is based will be given concurrently. Standard simplified statistical procedures (17) were followed. Values are reported as Means ± Standard Errors of the Means. Correlation of parameters will be shown in the scatter diagrams following the method of Olmstead and Tukey (10) whose table was also used to estimate statistical significance levels. In a few rats of large body weight correlated data were obtained by repeatedly sampling their peritoneal fluid over a period of a few months.

## RESULTS

Mast cells in rat peritoneal fluid expressed as cellular concentrations, absolute numbers within the cavity (concentration times total volume), and percentages of the total cellular population are given in figs. 1, 2, and 3, respectively. Morphologic aspects of the study are expressed as cellular size (fig. 4) and as percentages of the mast cell population displaying abnormal shapes (fig. 5).

It will be noted that mast cell concentrations in peritoneal fluid increase with body weight in the rat (fig. 1), and that this change represents an actual increase in absolute numbers of these cells within the peritoneal cavity (fig. 2). Both of these correlations are statistically significant at the 1 per cent level. When the data are expressed relatively to the total cellular population of peritoneal fluid, an increase is found in mast cell percentage with increasing body weight which is statistically significant at the 5 per cent level.

Morphologic changes are also apparent. The mean size of peritoneal fluid mast cells is positively correlated to body weight (fig. 4) as is also the relative incidence of abnormally-shaped cells (fig. 5). The changes revealed in both these parameters are statistically significant with a probability value well below 0.001. The abnormal forms encountered are identical

Submitted for publication March 2, 1956.

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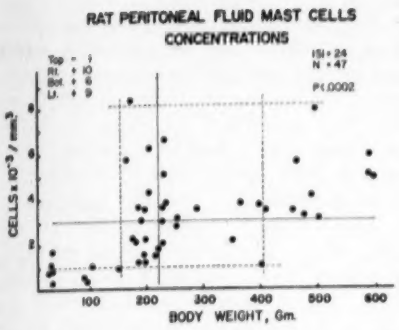


Fig. 1. Rat peritoneal fluid mast cell concentrations as a function of body weight.

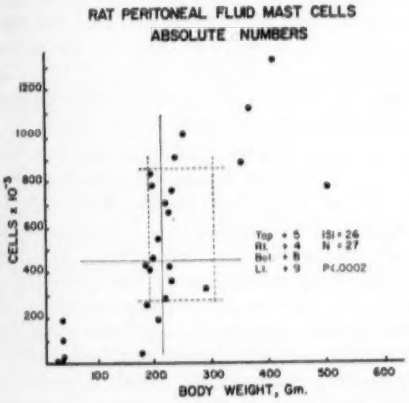


Fig. 2. Rat peritoneal fluid mast cells (absolute numbers within cavity) as a function of body weight.

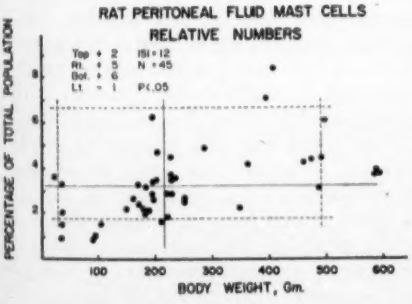


Fig. 3. Rat peritoneal fluid mast cell percentages as a function of body weight.

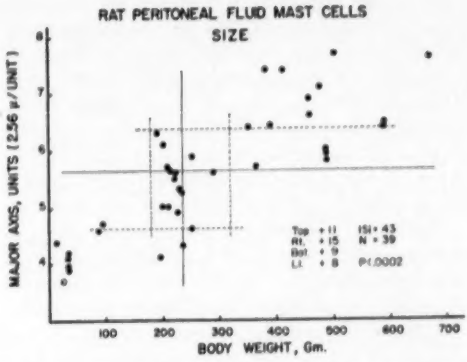


Fig. 4. Rat peritoneal fluid mast cell size as a function of body weight.

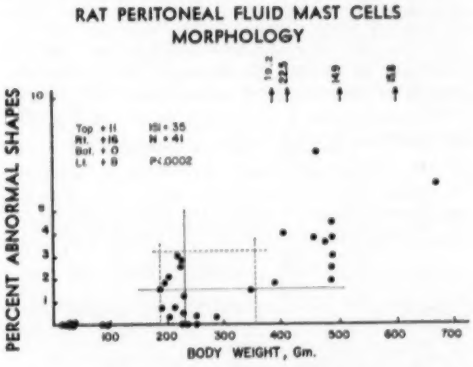


Fig. 5. Rat peritoneal fluid mast cells. Incidence of abnormal morphology as a function of body weight.

morphologically to those described by us following hypophysectomy (13). The majority of mast cells in peritoneal fluid of intact young adult rats (150-250 Gm.) are usually spherical or slightly ovoid. Abnormal cells assume irregular shapes characterized by striking elongation or budding of the granular cytoplasmic mass. The nucleus retains its approximately central position within the cytoplasm. No alterations in the staining properties with aqueous toluidine blue have been noted in these abnormal cells. Typical mast cells from young animals and abnormally shaped cells from old animals are shown in figure 6. As a rule, the degree of abnormality is greatest for very old animals with a progressive change being evident between the extremes of body weights represented in our experiments.

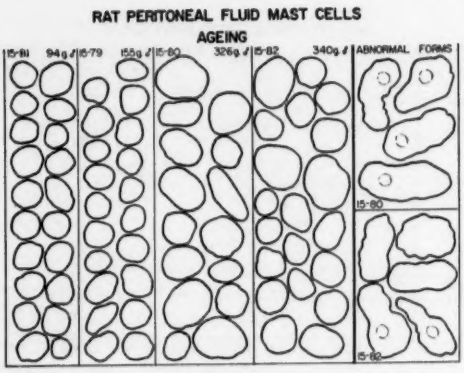


Fig. 6. Peritoneal fluid mast cell morphology in young adult and in older rats. Camera lucida drawings of mast cells in the hemacytometer. The 4 vertical columns at left represent mast cells drawn in the order encountered while the ones at the right represent selected abnormal shapes from the heavier two rats (# 15-80 and # 15-82). No abnormal forms were discernible in the two lighter animals (# 15-79 and # 15-81).

Magnification: 314 diameters.

TABLE 1. MAST CELL SIZE AND MORPHOLOGY IN CONSECUTIVE SAMPLES OF PERITONEAL FLUID OF AGING RATS.

| Sample Number | Date | Body Weight (Gm.) | Mast Cell Size, Units* | % Abnormal Forms |
|---|---|---|---|---|
| 53-7A | 11 June 54 | 488 | 6.0±0.204 | 4.5 |
| 7B | 26 Nov. 54 | 595 | 6.4±0.189 | 15.8 |
| 7E | 9 Feb. 55 | 675 | 7.6±0.220 | 6.2 |
| 53-8 | 31 Dec. 54 | 488 | 5.8±0.204 | 1.9 |
| 8A | 15 May 55 | 490 | 5.9±0.157 | 3.8 |
| 53-9 | 3 Jan. 55 | 456 | 6.9±0.220 | 3.8 |
| 9A | 15 May 55 | 460 | 6.6±0.204 | 7.6 |
| 53-10 | 3 Jan. 55 | 588 | 6.4±0.205 | 3.0 |
| 10A | 18 May 55 | 589 | 6.4±0.173 | 2.5 |
| 10B | 1 Nov. 55 | 407 | 7.4±0.205 | 4.0 |
| 53-16A | 16 May 55 | 477 | 7.1±0.205 | 3.6 |
| 16B | 3 Nov. 55 | 500 | 7.7±0.189 | 14.9 |

* Mean ± S. E. of Mean (for 50 cells) calculated from values for range /$\sigma$ (Snedecor, p. 98) where S. E. = $\frac{\text{range}}{(\text{range}/\sigma)\sqrt{N}}$

Repeated sampling of a given animal is practicable and presumably would eliminate variations among animals as a source of uncertainty in statistical evaluation of the data. The results for a few animals, followed in this way, are presented in table 1.

## DISCUSSION

In this paper, body weight has been considered as an index of age, an admittedly wanting procedure, but nevertheless adequate enough to suggest that long term studies should be conducted with animals of accurately known age. Even though correlations between given parameters and body weight can be demonstrated, it must be emphasized that this approach does not allow detailed interpretations of curve shapes, slopes, or intercepts except perhaps in very general terms and on a qualitative basis at best. Aging animals generally show body weight gains reaching a plateau which is maintained over a long period of their lifespan, and some very old animals have, according to our observations, actually lost weight in the last weeks of life.

Changes in mast cell concentrations as a function of age have been observed for both rat peritoneal fluid (18) and for connective tissues of several species (2, 4, 6, 7, 9, 16). The studies of Webb (18) covered only animals from 10 to 50 days postpartum.

It has been reported that fewer elements were seen in connective tissues of young animals than in the adult (16), while Bates (2) has noted that their numbers in 2-6 day old rats rapidly decreased to low levels which were then maintained up to 78 weeks of age. In statistical studies on human myocardium, Cairns and Constantinides (4) found no differences in mast cell concentrations in young and aged adults as long as atherosclerotic individuals were not included in the group. For the latter, fewer mast cells were found in both sexes, with the non-atherosclerotic males possessing even smaller numbers than non-atherosclerotic females. These studies were not reported in sufficient detail to ascertain whether the errors of tissue cell enumerations (9, 13) were avoided. In very carefully designed experiments, Hellström and Holmgren (9) found a decrease in mast cells (expressed per unit volume of tissue) with advancing age in human skin and heart tissue. It may be noted that this method of evaluating mast cell concentrations could be affected by differential degrees of shrinkage or swelling of the tissue during fixation, a factor which might be the result of physico-chemical changes accompanying the aging process. It is apparent that accurate quantitation of tissue cells is fraught with technical difficulties. The choice of peritoneal fluid and the techniques employed

in this study have obviated many of the errors and difficulties attending studies of tissue mast cells, but it is apparent that even our methods are not as yet free of uncontrolled factors.

Except for Webb's paper (18), all the above mentioned reports have pertained to mast cell counts performed on tissue sections. Mast cells are often distributed non-uniformly in tissues and, in addition, experimental treatments and histologic procedures may lead to generalized spatial changes within the tissues. Furthermore, mast cell morphology can best be studied in peritoneal fluid because the changes apparent in this site are not clearly evident in connective tissues. This dichotomy is probably the result of difference in the physico-chemical state of the respective environments (semigelatinous connective tissue versus fluid medium). These factors have been discussed in detail elsewhere (13).

The results indicate that mast cell numbers in peritoneal fluid generally increase with advancing age when expressed as either concentration, absolute numbers, or percentage of the total cellular population in male rats. For female rats, over the restricted body weight range available (120-240 Gm.), cellular concentrations and relative numbers of mast cells in virgin animals were 3,150 ± 356 /mm.$^3$ and 3.68 ± 0.56% respectively (35 animals) as compared to 3,340 ± 420 /mm.$^3$ and 3.14 ± 0.26% respectively (22 animals) for males of similar body weights. Even though these animals are of comparable weights, it is probable that the females are appreciably older. With aging, the increase in absolute numbers was perhaps to be anticipated as was the increase in amount of fluid present since this represents a component of growth of the animal. The increased cellular concentrations may represent relative dehydration of the connective tissue spaces (8) of which peritoneal fluid is a part.

Of greater interest are the morphologic alterations observed. Their parallelism to those seen following hypophysectomy in the rat suggests that perhaps the hypophysectomized animal ages more rapidly at the physiologic level. It is also possible that the old animal secretes inadequate amounts of the growth principle; it will be recalled (11, 13) that mast cells seem normal in hypophysectomized rats treated with growth hormone. The causation of the processes involved here is not clear, however, since both old age and hypophysectomy are attended by dysfunction of the gastro-intestinal tract probably accompanied with alterations in digestive and absorptive capacity. Growth hormone replacement treatment in hypophysectomized rats reestablishes the histologic integrity of the gastro-intestinal tract (1). The growth hormone preparation used in our studies when given to very old rats, and assessed in terms of peritoneal fluid mast cell morphology, has yielded equivocal results, but too few animals have been studied to date to permit any conclusions to be drawn at this time. Mast cells displaying abnormal shapes and unusually large size have been described in the bone marrow of an older patient (5) but the suggestion that mastocytosis was present seems insufficiently documented since the marrow was described as hypocellular. Data expressing mast elements as a percentage of a cellular population sampled from smear preparation may be unreliable since, even if mast cells were unaffected in total numbers, a concomitant reduction in bone marrow cellularity would be reflected as a rise in their percentage of the population. The morphologic characters of some cells in the illustrations of Cazal's paper (5) nevertheless closely resemble those seen in peritoneal fluid of old rats.

It should be emphasized that the morphologic changes described herein pertain to cellular populations as a whole and that there is no indication of whether cells are thus affected individually or are merely being replaced by a new population displaying the new characteristics. Aging of a particular cell usually involves enlargement of the cell body, especially its nucleus (8) and such information is not as yet available for mast elements. Cellular populations from the anterior pituitary and parathyroid glands of mice have been shown to be composed of progressively smaller elements with advancing age of the animal (3), in contrast to the increasing size of mast cells reported in this study for the rat. The size of glandular cells, however, is known to reflect their state of activity. Perhaps too little is understood at present about mast cells to know whether they should be likened to or contrasted with glandular cells in this respect.

The possibility exists that mast cells are affected differently depending on the site they occupy within the organism. We believe that this is not the case and that the effects ob-

served are referable to the cell itself. Thus, it may be that polymorphic mast cells of the mesenteries and serous membranes lining the cavity are shed into peritoneal fluid but, whereas mast cells of intact young rats readily round up once shed, those in old animals or in hypophysectomized rats do not. Further studies are in progress to elucidate this question as well as to assess the influence of growth hormone on connective tissues and the shedding process.

The study of mast cells may afford important clues as to the physiologic processes involved in aging. This warrants the expenditure of the additional time and effort entailed in sampling repeatedly the mast cells in animals over their entire lifespan.

## SUMMARY

Mast cells in peritoneal fluid have been studied in male rats of varying weights (ages). Increases in body weights are associated with increase in mast cellular concentrations, absolute numbers, and percentage of the total cellular population present. Morphologic alterations in mast cells, involving enlargement of the cell body and departure from their normally spherical or ovoid shape, are found with increasing frequency as body weight (age) increases. The significance of these changes are discussed. Repetition of these studies in animals of known age sampled throughout life would aid in the interpretation of the observed facts.

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# HEXOSAMINE AND ACID-HYDROLYZABLE SULFATE CONCENTRATIONS OF THE AORTA AND PULMONARY ARTERY IN INDIVIDUALS OF VARIOUS AGES*

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Reports in the literature on determinations of the hexosamine content and the concentration of acid-hydrolyzable sulfate in arterial tissue are few. Analyses performed by Kuzin and Gladyshev (8) on 4 samples of human aortic tissue revealed a hexosamine content ranging between 8.7 and 16.5 mg. per Gm. dry weight. Determinations of the concentration of acid-hydrolyzable sulfate in human aortic tissue have been reported by Faber (4), who studied 22 arterial samples derived from individuals ranging in age between 23 and 84 years. A sulfate ($SO_4$) concentration of 0.12 to 0.34 per cent, calculated on the basis of the dry tissue weight with a mean value of 0.23 per cent was found. No significant variation in the tissue sulfate concentration with age was observed.

The present study was undertaken with the purpose of providing analytical data on the hexosamine and acid-hydrolyzable sulfate concentrations of a larger number of samples of the aorta and pulmonary artery derived from individuals of various ages.

## METHODS

One hundred and twenty-four samples of the human aorta (thoracic descending) and 91 samples of the pulmonary artery were obtained fresh at autopsy at the St. Louis City Morgue†. The age of the individuals from whom the samples were obtained ranged between 5 weeks and 89 years. After separation of the adventitia, sections of the intima-media were employed for determination of hexosamine and acid-hydrolyzable sulfate.

*Determination of hexosamine.*—For determination of the hexosamine content of the tissue a 5 per cent homogenate of the arterial sample in distilled water was prepared. One ml. of the homogenate was pipetted into a 10 ml. glass ampoule and 1.0 ml. of 4 N hydrochloric acid added. The ampoule was sealed and subsequently heated for 2 hours in an electric oven at 118 C. After cooling, the contents of the ampoule were transferred quantitatively to a 10 ml. glass-stoppered volumetric flask, the ampoule being rinsed with several portions of distilled water. The sample in the volumetric flask was made up to 10 ml. volume with water, and, after mixing, filtered through a Whatman No. 40 filter paper.

The colorimetric hexosamine determinations were performed on 1.0 ml. aliquots of the filtrate, using the modification of Elson and Morgan's (3) procedure described by Boas (1). A reagent blank and a set of standards containing 10, 20, and 30 micrograms of glucosamine hydrochloride were run with each set of analyses. The acetylacetone and p-dimethylaminobenzaldehyde reagents employed in the method were prepared fresh daily. The readings were made at 530 millimicrons using a Coleman No. 14 spectrophotometer. For conversion of the hexosamine hydrochloride value to hexosamine the factor of 0.829 was used. All analyses were carried out in duplicate. The average difference between duplicate determinations was 2.9 per cent.

Experiments were carried out to establish the optimal hydrochloric acid concentration for hydrolysis of the arterial mucopolysaccharides and the time required for maximal hexosamine liberation. A final hydrochloric acid concentration of 2 N was found suitable. The results of hexosamine determinations following various periods of heating at 118 C. with this concentration of acid are shown in figure 1. It will be seen from the figure that a nearly maximal hexosamine liberation was obtained after 1 hour of heating and that heating for 2 and 3 hours gave the same hexosamine readings. It will further be noted that no destruction of hexosamine was observed following heating of a standard hexosamine solution for 4 hours

Submitted for publication April 12, 1956.

* Studies on Arterial Metabolism XIII. The investigation was supported by a grant ( PHS-891 ) from the National Heart Institute of the National Institutes of Health, Public Health Services.

† The authors are indebted to Dr. J. J. Connor for assistance in obtaining specimens.

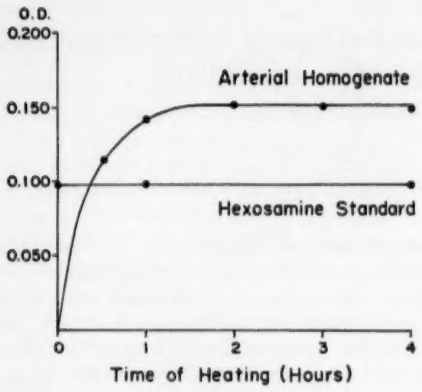


Fig. 1. Hexosamine values found in hydrolysates after heating of an arterial homogenate and a hexosamine standard solution with 2 N hydrochloric acid at 118 C. for various periods of time.

under the conditions of the procedure. Hexosamine added to arterial homogenates was recovered quantitatively.

Since it has been pointed out by Dische (2) that the demonstration of stability of free hexosamine during heating with acid does not necessarily prove that a destruction of hexosamine in linkage does not occur under the same conditions, determinations were made of the reducing power of the hydrolysates after various periods of heating. Such measurements, performed by the method of Nelson (10) with the reagents described by Somogyi (12), showed no increase in the reducing power of hydrolysates of human arterial tissue after 2 hours of heating with 2 N hydrochloric acid at 118 C. in experiments conducted for periods up to 8 hours.

In the analyses of the arterial homogenates, adsorption of the hydrolysates on a cation exchange resin and subsequent elution of the hexosamine prior to the colorimetric determination was not found necessary, since examination of the absorption spectrum of the color compound failed to disclose the presence of interfering chromogens (1).

*Determination of acid-hydrolyzable sulfate.*—For hydrolysis of the sulfate-containing mucopolysaccharides of the arterial tissue a 10 per cent homogenate of the tissue in redistilled water was prepared. Two ml. of the homogenate were pipetted into a 10 ml. glass ampoule and 2.0 ml. of concentrated hydrochloric acid were added. The ampoule was sealed and subsequently heated for 15 hours in an electric oven at 118 C.

After cooling, the contents of the ampoule were transferred quantitatively to a 20 ml. beaker, the ampoule being rinsed with two 1 ml. portions of redistilled water. Since chloride ions may interfere with the precipitation of sulfate as the benzidine compound, the hydrochloric acid of the sample was removed before the sulfate analysis. This was accomplished by evaporating the sample to dryness in a vacuum desiccator which contained a beaker with sodium hydroxide pellets for absorption of the hydrochloric acid vapors; anhydrous magnesium perchlorate, placed in the bottom of the desiccator, was used for absorption of the water.

For removal of phosphates prior to the precipitation of sulfate with benzidine the residue in the beaker was dissolved in 3.0 ml. of redistilled water, after which the pH of the solution was adjusted to 4-5, using external shielded glass electrodes. The sample was subsequently transferred to a graduated centrifuge tube and the beaker rinsed with three 1.0 ml. portions of redistilled water, which were added to the sample in the centrifuge tube. For precipitation of phosphates the method of Fiske (5) was used. A 10.5 per cent solution of ferric chloride in 0.1 N hydrochloric acid was added dropwise to the sample until no further precipitation occurred; this was followed by the addition of the same number of drops of a 10 per cent ammonium acetate solution. The sample was then centrifuged to remove the precipitate, after which the completeness of the phosphate removal was ascertained by addition of another drop of ferric chloride solution. The excess of ferric ions was finally removed by adding a drop of ammonium acetate solution and heating the sample to boiling in a water bath. After cooling, the volume of the sample was recorded and the solution filtered through a Whatman No. 40 filter paper.

Two 2.0 ml. aliquots of the phosphate-free filtrate were used for sulfate analysis. The sulfate determination was carried out essentially as described by Hoagland (6). Instead of subjecting the precipitated benzidine sulfate to gasometric carbon analysis, the precipitate was dissolved in 0.2 N hydrochloric acid and the benzidine concentration of the solution determined by ultraviolet spectrophotometry, using a Beckman DU spectrophotometer. The spec-

TABLE 1. HEXOSAMINE AND ACID-HYDROLYZABLE SULFATE CONCENTRATIONS OF 124 HUMAN AORTIC SAMPLES.

| No. | Age (Years) | Sex | Race | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Hexosamine, % of Wet Weight | Acid-Hydrol. $SO_4$, % of Wet Weight | Macroscopic Arteriosclerosis |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.1 | M | C | 29.4 | 4.63 | 0.39 | 0.29 | | none |
| 2 | 0.5 | M | W | 28.1 | 4.11 | | 0.27 | | none |
| 3 | 1 | F | W | 30.9 | 4.76 | 0.23 | 0.28 | 0.096 | none |
| 4 | 3 | M | W | 33.5 | 5.52 | 0.70 | 0.23 | | none |
| 5 | 3 | M | W | 36.3 | 5.17 | 0.35 | 0.30 | 0.046 | none |
| 6 | 3 | M | C | | | | 0.50 | 0.011 | none |
| 7 | 5 | M | W | 32.5 | 5.63 | 0.64 | 0.32 | 0.109 | none |
| 8 | 5 | F | C | 24.7 | 3.95 | 0.33 | 0.26 | 0.052 | none |
| 9 | 6 | M | W | | | 0.42 | 0.29 | 0.109 | none |
| 10 | 8 | F | W | 25.0 | 3.53 | 0.52 | 0.18 | 0.080 | none |
| | | Mean..... | | 30.1 | 4.41 | 0.45 | 0.29 | 0.072 | |
| 11 | 10 | F | C | 35.3 | 4.75 | 0.57 | 0.29 | 0.105 | none |
| 12 | 14 | M | W | 28.5 | 4.50 | 0.63 | 0.42 | | slight |
| 13 | 14 | M | W | 28.5 | 4.48 | 0.66 | 0.24 | | slight |
| 14 | 15 | F | C | 22.3 | 3.18 | 0.60 | 0.20 | 0.045 | slight |
| 15 | 16 | M | W | 28.7 | 4.13 | 0.68 | 0.38 | | slight |
| 16 | 16 | M | C | 29.8 | 4.21 | 0.55 | 0.32 | 0.082 | none |
| | | Mean..... | | 28.9 | 4.22 | 0.62 | 0.31 | 0.077 | |
| 17 | 21 | M | W | 27.4 | 4.32 | 1.17 | 0.37 | 0.096 | slight |
| 18 | 22 | F | C | 27.1 | 4.07 | 0.36 | 0.35 | 0.090 | slight |
| 19 | 24 | M | W | 29.4 | 4.38 | 1.11 | 0.20 | | moderate |
| 20 | 24 | M | W | 28.7 | 3.86 | 0.81 | 0.22 | 0.061 | moderate |
| 21 | 24 | F | W | 27.8 | 4.45 | 1.26 | 0.41 | | slight |
| 22 | 25 | M | C | 31.0 | 4.13 | 1.30 | 0.32 | 0.107 | slight |
| 23 | 25 | F | W | 27.7 | 4.80 | 0.68 | 0.37 | 0.110 | slight |
| 24 | 26 | M | W | 22.8 | 3.14 | 0.65 | 0.19 | 0.055 | none |
| 25 | 28 | M | C | 31.0 | 4.07 | 0.77 | 0.23 | 0.091 | slight |
| 26 | 29 | M | W | 30.2 | 4.03 | 0.58 | 0.37 | 0.087 | moderate |
| | | Mean..... | | 28.3 | 4.13 | 0.87 | 0.30 | 0.087 | |
| 27 | 31 | M | W | 25.1 | 3.80 | 0.80 | 0.32 | | slight |
| 28 | 31 | F | C | 34.6 | | 0.46 | | 0.078 | slight |
| 29 | 32 | F | W | 27.5 | 3.28 | 1.20 | 0.38 | 0.095 | slight |
| 30 | 32 | F | C | 31.7 | 4.34 | 0.67 | | 0.104 | slight |
| 31 | 33 | M | C | 26.3 | 3.30 | 1.28 | 0.27 | 0.083 | slight |
| 32 | 33 | M | C | 28.0 | 4.83 | 1.07 | | 0.078 | slight |
| 33 | 34 | M | W | 27.4 | 3.23 | 2.09 | 0.22 | 0.076 | slight |
| 34 | 37 | F | W | 28.7 | 3.10 | 0.76 | 0.37 | 0.091 | none |
| 35 | 38 | F | C | 29.3 | 4.30 | 1.41 | 0.47 | 0.089 | moderate |
| 36 | 39 | M | W | 27.8 | 3.49 | 1.92 | 0.28 | 0.082 | slight |
| 37 | 39 | F | C | 30.1 | 3.81 | 1.09 | 0.34 | 0.061 | slight |
| | | Mean..... | | 28.7 | 3.75 | 1.16 | 0.33 | 0.084 | |
| 38 | 40 | F | W | 28.3 | 3.71 | 0.90 | 0.29 | 0.072 | none |
| 39 | 40 | F | C | 24.9 | 3.35 | 1.32 | 0.25 | | slight |
| 40 | 41 | M | W | 29.4 | 3.49 | 0.71 | 0.38 | 0.070 | moderate |
| 41 | 42 | F | C | 25.2 | 2.85 | 1.97 | 0.29 | 0.083 | moderate |
| 42 | 43 | M | C | 24.3 | 3.21 | 1.05 | 0.28 | 0.102 | slight |
| 43 | 44 | M | W | 29.6 | 3.66 | 2.07 | 0.25 | 0.044 | moderate |
| 44 | 44 | M | C | 26.6 | 3.54 | 1.57 | 0.31 | 0.087 | slight |
| 45 | 45 | M | W | 29.0 | 3.99 | 1.48 | 0.32 | 0.088 | slight |
| 46 | 46 | M | W | 27.7 | 2.39 | 6.86 | 0.33 | 0.072 | severe |
| 47 | 46 | M | C | 25.4 | 3.26 | 0.64 | 0.23 | 0.058 | moderate |
| 48 | 47 | M | W | 22.4 | 3.40 | 1.34 | | 0.080 | moderate |
| 49 | 49 | M | W | 26.9 | 3.54 | 1.16 | 0.28 | 0.065 | moderate |
| 50 | 49 | M | W | 28.5 | 3.92 | 0.83 | 0.30 | 0.061 | slight |
| 51 | 49 | M | W | 25.3 | 3.13 | 1.02 | | 0.065 | slight |
| 52 | 49 | F | W | 28.1 | 3.45 | 1.20 | 0.26 | 0.060 | slight |
| 53 | 49 | F | C | 24.4 | 3.25 | 2.17 | 0.30 | 0.065 | moderate |
| | | Mean..... | | 26.7 | 3.39 | 1.64 | 0.29 | 0.072 | |
| 54 | 50 | M | W | 26.7 | 3.39 | 0.83 | 0.33 | 0.051 | moderate |
| 55 | 50 | F | W | 24.6 | 3.07 | 0.60 | 0.24 | 0.103 | moderate |
| 56 | 50 | F | W | 24.9 | 3.25 | 1.02 | 0.26 | 0.068 | slight |
| 57 | 50 | F | C | 30.5 | 3.02 | 1.01 | 0.31 | 0.047 | severe |
| 58 | 51 | M | W | 27.7 | 3.46 | 1.91 | 0.34 | 0.045 | severe |
| 59 | 52 | M | W | 24.0 | 3.39 | 2.18 | 0.22 | | moderate |
| 60 | 52 | M | W | 22.8 | 3.05 | 1.36 | 0.23 | 0.067 | moderate |
| 61 | 52 | M | W | 23.8 | 2.56 | 1.09 | | 0.054 | moderate |
| 62 | 52 | M | C | 29.3 | 3.88 | 1.88 | 0.22 | 0.078 | slight |
| 63 | 53 | M | W | 26.3 | 3.63 | 3.29 | 0.28 | 0.058 | moderate |
| 64 | 53 | M | W | 30.1 | 3.43 | 1.68 | 0.34 | 0.075 | slight |
| 65 | 53 | F | W | 24.2 | 3.26 | 1.10 | 0.33 | | slight |
| 66 | 53 | F | W | 23.5 | 3.23 | 1.89 | 0.37 | 0.071 | moderate |
| 67 | 53 | F | W | 28.6 | 3.35 | 1.31 | 0.36 | 0.091 | slight |
| 68 | 53 | F | C | 26.9 | 3.52 | 1.49 | 0.30 | 0.096 | severe |
| 69 | 53 | F | C | 28.5 | 3.46 | 0.98 | 0.43 | 0.120 | slight |
| 70 | 54 | M | W | 26.0 | 3.37 | 1.68 | 0.17 | 0.034 | moderate |
| 71 | 54 | M | W | 23.2 | 3.02 | 2.08 | 0.27 | 0.100 | moderate |
| 72 | 54 | M | C | 26.2 | 3.40 | 2.95 | 0.26 | 0.040 | moderate |
| 73 | 55 | M | W | 27.0 | 3.68 | 1.40 | 0.29 | 0.103 | slight |
| 74 | 55 | M | W | 24.8 | 3.11 | 1.39 | 0.28 | 0.070 | moderate |
| 75 | 55 | M | W | 29.1 | 3.85 | 1.45 | 0.33 | 0.119 | slight |
| 76 | 55 | M | C | 29.8 | 3.24 | 6.16 | 0.30 | 0.103 | severe |
| 77 | 55 | M | C | 26.4 | 3.49 | 0.87 | 0.29 | 0.066 | moderate |
| 78 | 56 | M | W | 26.8 | 3.88 | 3.71 | 0.36 | 0.066 | moderate |
| 79 | 56 | F | W | 28.2 | 3.56 | 2.24 | 0.36 | | moderate |
| 80 | 57 | M | W | 31.2 | 3.25 | 5.12 | 0.23 | 0.091 | severe |
| 81 | 57 | M | W | 33.3 | 3.92 | 1.59 | 0.26 | 0.113 | severe |
| 82 | 57 | M | W | 27.9 | 3.25 | 2.15 | 0.23 | 0.094 | moderate |
| 83 | 57 | M | C | 25.9 | 3.03 | 1.94 | 0.25 | 0.056 | moderate |
| 84 | 57 | F | C | 23.6 | 3.44 | 1.36 | | 0.083 | slight |
| 85 | 58 | M | W | 29.8 | 2.51 | 8.70 | 0.36 | 0.042 | severe |
| 86 | 58 | M | W | 28.2 | 3.80 | 1.14 | 0.35 | 0.097 | none |
| 87 | 58 | M | C | 28.6 | 3.57 | 1.86 | 0.48 | 0.069 | moderate |
| 88 | 59 | M | C | 26.8 | 3.63 | 1.19 | 0.35 | 0.064 | moderate |
| | | Mean..... | | 27.0 | 3.37 | 2.08 | 0.30 | 0.077 | |
| 89 | 60 | M | W | 23.5 | 3.21 | 3.53 | 0.26 | | severe |
| 90 | 60 | M | W | 25.1 | 3.40 | 2.00 | 0.33 | 0.065 | severe |
| 91 | 61 | M | W | 28.3 | 2.72 | 4.19 | | 0.036 | severe |
| 92 | 61 | F | W | 26.9 | 3.31 | 1.04 | 0.39 | | none |
| 93 | 61 | F | W | 26.3 | 3.53 | 1.56 | 0.23 | | moderate |
| 94 | 62 | M | W | 29.4 | 3.72 | 2.95 | 0.23 | 0.072 | moderate |
| 95 | 62 | F | W | 27.3 | 2.84 | 3.95 | 0.27 | 0.053 | severe |
| 96 | 63 | M | W | 26.9 | 3.21 | 4.95 | 0.31 | 0.066 | severe |
| 97 | 64 | M | W | 26.4 | 3.44 | 3.12 | 0.34 | | moderate |
| 98 | 64 | M | W | 26.5 | 3.28 | 2.23 | 0.30 | 0.066 | moderate |
| 99 | 64 | M | W | 29.1 | 4.50 | 0.99 | | 0.075 | severe |
| 100 | 65 | M | W | 30.2 | 2.94 | 4.76 | 0.16 | 0.023 | severe |
| 101 | 65 | M | C | 30.2 | 2.01 | 3.83 | 0.18 | 0.050 | severe |
| 102 | 66 | M | W | 30.5 | 3.42 | 1.41 | 0.29 | 0.065 | slight |
| 103 | 66 | M | W | | | | 0.33 | | severe |
| 104 | 68 | M | W | 26.5 | 3.27 | 1.63 | 0.28 | 0.068 | moderate |
| 105 | 68 | F | W | 30.5 | 2.90 | | 0.29 | 0.089 | severe |
| 106 | 69 | M | W | 25.1 | 3.54 | 1.75 | 0.32 | 0.054 | moderate |
| 107 | 69 | M | W | 36.1 | 3.87 | 1.19 | 0.41 | 0.057 | severe |
| | | Mean..... | | 28.0 | 3.29 | 2.66 | 0.29 | 0.060 | |

TABLE 1. (CONTINUED).

| No. | Age (Years) | Sex | Race | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Hexosamine, % of Wet Weight | Acid-Hydrol. $SO_4$, % of Wet Weight | Macroscopic Arteriosclerosis |
|---|---|---|---|---|---|---|---|---|---|
| 108 | 70 | M | W | 24.7 | 3.42 | 1.87 | 0.36 | 0.091 | moderate |
| 109 | 70 | M | W | 24.4 | 3.25 | 1.88 | 0.24 | 0.063 | moderate |
| 110 | 71 | M | W | 28.0 | 3.24 | 0.69 | 0.33 | 0.084 | moderate |
| 111 | 72 | M | W | 26.4 | 3.27 | 3.45 | 0.30 | | severe |
| 112 | 72 | M | W | 30.0 | 3.94 | 2.82 | | 0.135 | severe |
| 113 | 72 | F | W | 23.3 | 2.93 | 2.40 | 0.28 | | severe |
| 114 | 75 | M | C | 24.1 | 3.33 | 0.72 | | 0.044 | slight |
| 115 | 76 | M | W | 34.4 | 2.46 | 3.18 | 0.32 | 0.083 | severe |
| 116 | 76 | M | W | 26.5 | 3.33 | 1.32 | 0.26 | 0.050 | moderate |
| 117 | 76 | F | W | 29.6 | 3.30 | 1.93 | 0.25 | 0.097 | severe |
| 118 | 77 | F | W | 37.2 | 2.62 | 3.68 | 0.29 | 0.095 | severe |
| 119 | 79 | F | W | 25.7 | 3.29 | 2.03 | 0.30 | 0.049 | severe |
| | | Mean..... | | 27.9 | 3.20 | 2.17 | 0.29 | 0.079 | |
| 120 | 80 | M | W | 27.3 | 3.44 | 1.96 | 0.28 | 0.074 | moderate |
| 121 | 82 | M | W | 30.1 | 3.78 | 2.62 | 0.38 | | slight |
| 122 | 87 | F | W | 25.0 | 3.50 | 1.55 | 0.20 | | severe |
| 123 | 88 | M | W | 23.0 | 2.70 | 1.20 | 0.25 | | moderate |
| 124 | 89 | F | W | 70.5 | 1.25 | 6.55 | 0.17 | 0.145 | severe |
| | | Mean..... | | 35.2 | 2.93 | 2.77 | 0.26 | 0.110 | |
| | | Grand Mean | | 28.1 | 3.53 | 1.78 | 0.30 | 0.075 | |

trophotometric sulfate determination, developed by the authors, will be described in detail in another publication. Blank determinations on both the hydrolysis and the sulfate analysis were carried out in connection with the sample analyses. All determinations were performed in duplicate. The average difference between duplicate analyses was 3.8 per cent.

TABLE 2. MEAN HEXOSAMINE AND ACID-HYDROLYZABLE SULFATE VALUES OF HUMAN AORTIC AND PULMONARY ARTERY SAMPLES IN VARIOUS DECADES.

| Age Group (Years) | Aorta | | | | Pulmonary Artery | | | |
|---|---|---|---|---|---|---|---|---|
| | Hexosamine | | Acid-Hydrol. $SO_4$ | | Hexosamine | | Acid-Hydrol. $SO_4$ | |
| | % of Wet Weight | % of Dry Weight | % of Wet Weight | % of Dry Weight | % of Wet Weight | % of Dry Weight | % of Wet Weight | % of Dry Weight |
| 0– 9 | 0.29 | 0.90 | 0.072 | 0.261 | 0.26 | 1.07 | 0.064 | 0.254 |
| 10–19 | 0.31 | 1.08 | 0.077 | 0.259 | 0.28 | 1.05 | 0.048 | 0.205 |
| 20–29 | 0.30 | 1.07 | 0.087 | 0.308 | 0.30 | 1.11 | 0.066 | 0.245 |
| 30–39 | 0.33 | 1.19 | 0.084 | 0.289 | 0.27 | 1.02 | 0.056 | 0.221 |
| 40–49 | 0.29 | 1.08 | 0.072 | 0.272 | 0.25 | 1.00 | 0.060 | 0.245 |
| 50–59 | 0.30 | 1.12 | 0.077 | 0.282 | 0.28 | 1.14 | 0.075 | 0.309 |
| 60–69 | 0.29 | 1.04 | 0.060 | 0.212 | 0.28 | 1.10 | 0.080 | 0.339 |
| 70–79 | 0.29 | 1.07 | 0.079 | 0.277 | 0.29 | 1.26 | 0.081 | 0.351 |
| 80–89 | 0.26 | 0.89 | 0.110 | 0.238 | 0.26 | 1.23 | 0.039 | 0.180 |

Experiments were conducted to establish the time required for maximal liberation of sulfate. It was found that 93 per cent of the sulfate was liberated after 4 hours, 97 per cent after 7 hours, and 100 per cent after 15 hours' heating with hydrochloric acid. Sulfate added to the arterial homogenates before hydrolysis was recovered quantitatively. It was ascertained that the results of the spectrophotometric sulfate determinations agreed closely with sulfate analyses performed concomitantly by the gravimetric barium sulfate method.

In the case of both the aortic and pulmonary artery samples, determinations of the dry weight, total nitrogen, and cholesterol content of the tissue were made on a portion of the arterial wall adjacent to that employed for hexosamine and sulfate analyses. The nitrogen analyses were carried out by conventional Kjeldahl procedure. For the cholesterol determinations the procedure of Knobil and associates (7) was used.

## RESULTS

*Aortic samples.*—The results of the determinations of hexosamine (N=113) and acid-hydrolyzable sulfate (N=101) on the individual aortic samples are presented in table 1, and the mean values observed for the various decades are listed in table 2. The average hexosamine concentration found in the aortic tissue was 0.30 per cent (s.d. of distribution, 0.067), calculated on the basis of wet tissue weight. If expressed on the basis of dry tissue weight, the mean hexosamine concentration for the samples was 1.07 per cent. An analysis of the hexosamine values recorded for the two sexes revealed a mean hexosamine concentration for the women which was 103 per cent of that found for the men. As seen from table 2 no significant variation in the tissue concentration of hexosamine with age was observed.

With regard to the acid-hydrolyzable sulfate content of the aortic tissue, the average concentration found was 0.075 per cent (s.d. of distribution 0.023), calculated on the basis of wet tissue weight, and 0.270 per cent, expressed on the basis of dry tissue weight. The mean sulfate value found for the women was 116 per cent of that observed for the men; the t value for this difference is 2.18 (df 99). As in the case of the hexosamine values no significant variation in the tissue concentration of sulfate with age was noted (table 2).

TABLE 3. MEAN CHOLESTEROL, HEXOSAMINE, AND ACID-HYDROLYZABLE SULFATE VALUES OF AORTIC SAMPLES WITH VARIOUS DEGREES OF ARTERIOSCLEROSIS (AGE GROUP, 55-89 YEARS).

| Degree of Macroscopic Arteriosclerosis | Number of Samples | Mean Cholesterol Content | | Mean Hexosamine Content | | Mean Acid-Hydrol. Sulfate Content | |
|---|---|---|---|---|---|---|---|
| | | % of Wet Weight | % of Dry Weight | % of Wet Weight | % of Dry Weight | % of Wet Weight | % of Dry Weight |
| None or slight | 8 | 1.39 | 4.95 | 0.34 | 1.19 | 0.085 | 0.314 |
| Moderate | 20 | 1.88 | 7.00 | 0.30 | 1.13 | 0.070 | 0.262 |
| Severe | 24 | 3.38 | 11.74 | 0.28 | 0.94 | 0.077 | 0.240 |

An investigation was made of the correlation between the tissue cholesterol content and the hexosamine and sulfate concentrations of the samples derived from individuals between 55 and 89 years of age. The r values found for these correlations were, respectively, $-0.15$ ($N=45$, $t=0.99$) and $-0.02$ ($N=40$, $t=0.12$).

If, instead of the cholesterol concentration, the macroscopic grading of the samples was employed as an expression of the degree of arteriosclerosis, the mean hexosamine and sulfate values listed in table 3 were found.

A statistical evaluation of the hexosamine and sulfate values for the 3 groups of samples showed the difference between the mean hexosamine content of the samples with "none" or "slight" arteriosclerosis and of the samples with "severe" arteriosclerosis to be significant at the 5 per cent level of confidence, both when calculated on the basis of wet ($t=2.21$, df 25) and dry ($t=2.11$, df 24) tissue weight. A significant difference was also found between the dry weight hexosamine mean of 1.13 per cent for the samples characterized as having "moderate" arteriosclerosis and the mean of 0.94 per cent for the samples with "severe" arteriosclerosis ($t=2.36$, df 37). No statistically significant differences were found between the mean sulfate values of the 3 groups of aortic samples.

A comparison was further made of the hexosamine and sulfate values for the aortic samples of the 55-89 year age group in which a notable degree of calcification of the vessel wall was present and the samples which did not show macroscopic signs of calcification. Of the 52 samples in this age group 21 had calcified plaques.

The average hexosamine concentration of the calcified samples was 0.28 per cent (wet weight) and of the samples without macroscopic calcification, 0.30 per cent. The difference between these means was found not to be statistically significant ($t=1.02$, df 45). If, however, the hexosamine concentration of the dry tissue was used for comparison a significant difference between the mean value for the calcified (0.95 per cent) and the non-calcified (1.13 per cent) samples was found ($t=2.50$, df 44).

With regard to the concentration of acid-hydrolyzable sulfate the calcified samples showed a mean value of 0.081 per cent (wet weight) and the non-calcified a mean of 0.072 per cent. The t value for this difference is 1.08 (df 39). No significant difference was found either between the mean sulfate values of the 2 groups of samples when the sulfate concentrations of the dry tissue were employed for the calculation (mean value of calcified samples, 0.248 per cent; of non-calcified samples, 0.265 per cent; t of difference, 0.68, df 39).

*Pulmonary artery samples.*—The results of the determinations of hexosamine ($N=85$) and acid-hydrolyzable sulfate ($N=68$) carried out on the pulmonary artery samples are shown in table 4. The average hexosamine concentration found was 0.27 per cent (s.d. of distribution, 0.052), calculated on the basis of wet tissue weight, and 1.12 per cent, expressed on the basis of dry tissue weight. The same mean concentrations were recorded for the samples derived from the men and the women.

The average concentration of acid-hydrolyzable sulfate observed in the pulmonary artery tissue was 0.070 per cent (s.d. of distribution, 0.021), calculated on the basis of wet tissue weight (0.291 per cent, expressed on the basis of dry tissue weight). The mean sulfate value recorded for the women was 96 per cent of that found in the samples derived from the male subjects.

The average hexosamine and sulfate values observed for the various decades have been

TABLE 4. HEXOSAMINE AND ACID-HYDROLYZABLE SULFATE CONCENTRATIONS OF 91 HUMAN PULMONARY ARTERY SAMPLES.

| No. | Age (Years) | Sex | Race | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Hexosamine, % of Wet Weight | Acid-Hydrol. $SO_4$, % of Wet Weight | Macroscopic Arteriosclerosis |
|---|---|---|---|---|---|---|---|---|---|
| 5 | 3 | M | W | 25.9 | 3.85 | 0.79 | 0.36 | 0.058 | none |
| 6 | 3 | M | C | 25.0 | 3.60 | | 0.33 | 0.069 | none |
| 7 | 5 | M | W | 23.9 | 2.12 | 0.38 | 0.17 | 0.054 | none |
| 9 | 6 | M | W | | | | | 0.070 | none |
| 10 | 8 | F | W | 22.7 | 3.03 | 0.57 | 0.19 | 0.066 | none |
| | | Mean..... | | 24.4 | 3.15 | 0.58 | 0.26 | 0.064 | |
| 11 | 10 | F | C | 25.1 | 3.24 | 0.32 | | 0.054 | none |
| 12 | 14 | M | W | 29.3 | 4.58 | | 0.26 | | none |
| 13 | 14 | M | W | 27.7 | 4.05 | | 0.42 | | none |
| 14 | 15 | F | C | 21.6 | 3.01 | 0.51 | 0.16 | 0.042 | none |
| | | Mean..... | | 24.9 | 3.87 | 0.42 | 0.28 | 0.048 | |
| 17 | 21 | M | W | 25.0 | 4.02 | 0.52 | 0.37 | | none |
| 18 | 22 | F | C | | | | 0.31 | | slight |
| 21 | 24 | F | W | 26.5 | 4.15 | 0.87 | 0.33 | | none |
| 22 | 25 | M | C | 29.7 | 4.24 | 0.40 | 0.26 | 0.068 | none |
| 23 | 25 | F | W | | | | 0.31 | | none |
| 25 | 28 | M | C | 29.6 | 3.94 | | 0.27 | | none |
| 26 | 29 | M | W | 24.1 | 3.53 | 0.38 | 0.25 | 0.063 | none |
| | | Mean..... | | 27.0 | 3.98 | 0.54 | 0.30 | 0.066 | |
| 27 | 31 | M | W | 20.9 | 3.02 | 0.71 | 0.23 | | none |
| 28 | 31 | F | C | 25.6 | 3.24 | 0.24 | 0.18 | 0.052 | none |
| 30 | 32 | F | C | 23.5 | 2.72 | 0.29 | | 0.044 | none |
| 31 | 33 | M | C | 22.6 | 3.05 | 0.67 | 0.20 | 0.066 | none |
| 34 | 37 | F | C | 26.0 | 3.80 | | 0.36 | | none |
| 35 | 38 | F | C | 26.9 | 3.53 | 0.44 | 0.35 | 0.076 | none |
| 36 | 39 | M | W | 26.5 | 3.70 | 0.98 | 0.21 | | slight |
| 37 | 39 | F | C | 27.4 | 3.67 | 0.39 | 0.27 | 0.039 | none |
| | | Mean..... | | 25.0 | 3.34 | 0.53 | 0.27 | 0.056 | |
| 39 | 40 | F | C | 27.6 | 3.57 | 2.32 | 0.32 | 0.083 | none |
| 40 | 41 | M | W | 28.0 | | 0.68 | 0.34 | 0.057 | moderate |
| 42 | 43 | M | C | | | 0.93 | 0.28 | | slight |
| 43 | 44 | M | W | 25.3 | 3.54 | 1.21 | 0.26 | 0.061 | slight |
| 44 | 44 | M | C | 24.6 | 3.44 | 0.71 | 0.24 | | none |
| 45 | 45 | M | W | 26.1 | 3.66 | 0.82 | 0.26 | | none |
| 46 | 46 | M | W | 24.9 | 3.20 | 0.92 | 0.23 | 0.059 | slight |
| 47 | 46 | M | C | 24.8 | 3.48 | 0.41 | 0.18 | 0.044 | slight |
| 48 | 47 | M | W | 25.3 | 3.84 | | 0.26 | | slight |
| 49 | 49 | M | W | 26.4 | 3.48 | 0.65 | 0.26 | 0.060 | slight |
| 50 | 49 | M | W | 17.1 | 2.30 | | 0.17 | 0.053 | none |
| 52 | 49 | F | W | 23.7 | 2.90 | 0.46 | 0.23 | 0.063 | none |
| | | Mean..... | | 24.9 | 3.34 | 0.91 | 0.25 | 0.060 | |
| 54 | 50 | M | W | 26.9 | 3.36 | 0.82 | 0.30 | 0.066 | slight |
| 55 | 50 | F | W | 26.2 | 3.38 | 0.25 | 0.24 | 0.071 | none |
| 56 | 50 | F | W | 20.3 | 2.81 | 0.68 | 0.21 | | none |
| 57 | 50 | F | C | 23.7 | 2.66 | 0.61 | 0.32 | 0.071 | moderate |
| 58 | 51 | M | W | 26.7 | 3.29 | 0.39 | 0.19 | 0.040 | slight |
| 60 | 52 | M | W | 22.5 | 2.78 | 0.67 | 0.28 | 0.102 | none |
| 62 | 52 | M | C | 26.1 | 3.67 | 0.81 | 0.32 | 0.074 | none |
| 63 | 53 | M | W | 24.2 | 3.37 | 0.59 | 0.25 | 0.057 | slight |
| 64 | 53 | M | W | 27.2 | 3.85 | 1.22 | 0.27 | 0.074 | none |
| 65 | 53 | F | W | 23.2 | 3.57 | 0.80 | | 0.064 | none |
| 66 | 53 | F | W | 23.2 | 3.39 | 0.81 | 0.30 | 0.065 | slight |
| 68 | 53 | F | C | 23.9 | 3.37 | 0.83 | 0.30 | 0.081 | moderate |
| 69 | 53 | F | C | 23.9 | 3.29 | 0.57 | 0.28 | 0.090 | slight |
| 71 | 54 | M | W | 23.7 | 3.04 | 0.77 | 0.22 | 0.080 | none |
| 72 | 54 | M | C | 19.5 | 2.67 | 0.50 | 0.23 | 0.050 | none |
| 73 | 55 | M | W | 26.0 | 3.56 | 0.78 | 0.25 | 0.064 | none |
| 74 | 55 | M | W | 23.9 | 2.87 | 0.73 | 0.29 | 0.055 | slight |
| 75 | 55 | M | W | 25.2 | 3.07 | 0.81 | 0.28 | 0.099 | none |
| 78 | 56 | M | W | 21.9 | 3.37 | 2.85 | 0.29 | | slight |
| 79 | 56 | F | W | 28.4 | 3.76 | 0.72 | 0.27 | 0.081 | slight |
| 80 | 57 | M | W | 26.9 | 3.66 | 0.62 | 0.27 | 0.114 | moderate |
| 81 | 57 | M | W | 23.6 | 3.07 | 0.39 | 0.22 | 0.054 | slight |
| 82 | 57 | M | W | 20.6 | 2.48 | 0.56 | | 0.079 | slight |
| 85 | 58 | M | W | 21.6 | 3.00 | 2.50 | 0.35 | 0.085 | moderate |
| 86 | 58 | M | W | 24.3 | 3.41 | 0.92 | 0.31 | 0.139 | none |
| 87 | 58 | M | C | 24.9 | 3.26 | 0.91 | 0.32 | 0.067 | slight |
| 88 | 59 | M | C | 24.1 | 3.30 | 0.77 | 0.34 | 0.070 | slight |
| | | Mean..... | | 24.2 | 3.24 | 0.85 | 0.28 | 0.075 | |
| 92 | 61 | F | W | 18.9 | | 0.37 | | 0.109 | none |
| 93 | 61 | F | W | 24.0 | 2.93 | 1.01 | 0.22 | 0.052 | slight |
| 94 | 62 | M | W | 26.6 | 3.70 | 1.08 | 0.25 | 0.074 | slight |
| 95 | 62 | F | W | 22.4 | 3.29 | 1.75 | 0.24 | 0.088 | none |
| 96 | 63 | M | W | 23.9 | 3.62 | 1.84 | 0.31 | | slight |
| 97 | 64 | M | W | 21.6 | 3.13 | 1.32 | 0.33 | | slight |
| 98 | 64 | M | W | 23.9 | 3.20 | 1.27 | 0.28 | 0.109 | slight |
| 99 | 64 | M | W | 24.7 | 2.98 | 0.37 | 0.26 | 0.090 | slight |
| 100 | 65 | M | W | 23.6 | 3.31 | 1.43 | 0.23 | 0.047 | slight |
| 101 | 65 | M | C | 25.8 | 3.80 | 1.36 | 0.29 | 0.112 | moderate |
| 102 | 66 | M | W | 26.4 | 4.11 | 0.85 | 0.26 | 0.087 | slight |
| 104 | 68 | M | W | 23.0 | 2.99 | 0.86 | 0.26 | 0.068 | slight |
| 105 | 68 | F | W | 24.7 | 3.33 | 1.60 | 0.25 | 0.078 | slight |
| 106 | 69 | M | W | 38.7 | 5.60 | 1.49 | 0.33 | | slight |
| 107 | 69 | M | W | 24.6 | 3.15 | 0.63 | 0.34 | 0.052 | moderate |
| | | Mean..... | | 24.8 | 3.51 | 1.15 | 0.28 | 0.080 | |
| 108 | 70 | M | W | 21.2 | 2.96 | 1.75 | 0.36 | 0.091 | slight |
| 109 | 70 | M | W | 23.2 | | 0.96 | 0.30 | | slight |
| 110 | 71 | M | W | 23.2 | 2.86 | | 0.25 | 0.077 | slight |
| 115 | 76 | M | W | 23.2 | 2.92 | 0.65 | 0.26 | 0.072 | slight |
| 116 | 76 | M | W | 21.8 | 2.78 | 0.98 | 0.20 | 0.063 | slight |
| 117 | 76 | F | W | 23.7 | 3.22 | 0.59 | 0.29 | 0.077 | slight |
| 118 | 77 | F | W | 20.9 | 2.88 | 0.54 | 0.31 | | moderate |
| 119 | 79 | F | W | 24.8 | 3.26 | 1.19 | 0.33 | 0.104 | slight |
| | | Mean..... | | 22.8 | 2.98 | 0.95 | 0.29 | 0.081 | |
| 120 | 80 | M | W | 22.3 | 3.08 | 0.68 | 0.23 | 0.057 | none |
| 121 | 82 | M | W | 20.7 | 3.57 | 1.60 | 0.28 | | slight |
| 122 | 87 | F | W | | | | 0.24 | | slight |
| 123 | 88 | M | W | 20.0 | 2.92 | 1.20 | 0.27 | 0.044 | slight |
| 124 | 89 | F | W | 23.6 | 2.69 | 0.90 | 0.28 | 0.015 | moderate |
| | | Mean..... | | 21.7 | 3.07 | 1.10 | 0.26 | 0.039 | |
| | | Grand Mean | | 24.5 | 3.36 | 0.87 | 0.27 | 0.070 | |

included in table 2. As seen from the data listed in the table no significant variation in the tissue hexosamine concentration was noted with age.

In contrast to this the acid-hydrolyzable sulfate values of the pulmonary artery tissue were in general found to be higher for the 50-79 year age group than for younger individuals. Thus the mean sulfate concentration for the 50-79 year old subjects was 0.078 per cent (wet weight) and for the 3-49 year old individuals 0.059 per cent. The t value for this difference is 3.83 (df 63). Significantly higher sulfate values were also found for the 50-79 year group when the sulfate concentrations were expressed on the basis of dry tissue weight (mean sulfate concentration for the 50-79 year group, 0.324 per cent; for the 3-49 year group, 0.237 per cent; t value of difference, 4.06, df 62). The difference in the average sulfate values for the 2 age groups was evident both for the men and the women.

As in the case of the aortic samples an analysis was made of the correlation between the tissue cholesterol content and the hexosamine and sulfate concentrations for the pulmonary artery samples derived from individuals between 55 and 89 years of age. The r values found for these correlations were, respectively, +0.18 (N=36, t=1.05), and +0.10 (N=31, t=0.54).

## DISCUSSION

The hexosamine and acid-hydrolyzable sulfate concentrations of the arterial tissue observed in the present study are of the same order of magnitude as the values reported by previous investigators (4, 8). The sulfate present in the acid hydrolysates is considered to be derived chiefly from sulfate-containing mucopolysaccharides, presumably chondroitin sulfates, the concentration of free sulfate in the tissue being negligible. According to the formula given by Levene (9) chondroitin sulfate contains 18.75 per cent sulfate ($SO_4$) and 35.0 per cent hexosamine. If the assumption is made that all the acid-hydrolyzable sulfate found in the tissue represents chondroitin sulfate, the quantity of hexosamine present as chondroitin sulfate may be calculated by multiplying the acid-hydrolyzable sulfate value with 1.86.

It is of interest to note that in nearly all the arterial samples studied a concentration of hexosamine in the tissue was found which was considerably in excess of that which could be accounted for on the basis of the values for acid-hydrolyzable sulfate. Such discrepancy is also apparent when the sulfate values for aortic tissue reported by Faber (4) and the hexosamine concentrations found by Kuzin and Gladyshev (8) are compared. The nature of the hexosamine which is not present as a component of chondroitin sulfate has not been determined. In the present studies the concentration of non-chondroitin sulfate hexosamine averaged 0.160 per cent in the aortic tissue and 0.135 per cent in the pulmonary artery tissue, when calculated on the basis of wet tissue weight. These concentrations are, respectively, 54 and 50 per cent of the total hexosamine values found.

The present investigation showed no significant variation with age in the hexosamine and acid-hydrolyzable sulfate concentrations of the aortic samples. In the case of the pulmonary artery samples the hexosamine concentration likewise remained essentially unchanged with age, whereas higher tissue sulfate values were found in samples derived from individuals aged 50-79 years than in younger subjects. The significance of this increase in tissue sulfate concentration is not apparent.

The analyses performed on the correlation between the degree of arteriosclerosis present in aortic samples derived from middle-aged and old individuals and the hexosamine and sulfate concentrations of the tissue failed to show a significant relation between the cholesterol content of the vessel wall and the concentrations of these compounds. A possibly significant difference was noted between the hexosamine content of the aortic samples classified as having "none," "slight," and "moderate" arteriosclerosis, and the concentration of the samples found to be the site of "severe" arteriosclerosis, the latter specimens showing the lower hexosamine values. Since, however, the evaluation of the degree of arteriosclerosis for this comparison was based on a subjective judgment, and not on objective measurements, the importance of this finding remains uncertain. The fact that an accumulation of deposits of non-mucopolysaccharide character in the severely arteriosclerotic vessels in itself would contribute to lower hexosamine values must also be considered in this connection. The lower hexosamine values found in the calcified aortic samples as compared with the non-calcified specimens may

similarly be explained by such deposits, at least partly. It should be noted, however, that some of the severely arteriosclerotic and calcified samples showed hexosamine (and sulfate) concentrations well above the average and that the values for the specimens with a high degree of arteriosclerosis showed greater variation than the values for arteries with a minor degree of arteriosclerosis.

The failure to demonstrate any positive correlation between the tissue cholesterol content and the degree of macroscopic arteriosclerosis on one side and the hexosamine and sulfate concentrations on the other side for aortic samples obtained from middle-aged and old subjects would seem to be of importance, since the occurrence of increased amounts of metachromatic tissue has been found by several investigators (11, 13) in the presence of arteriosclerotic changes. In view of the findings of this study it seems likely that an alteration in the staining behavior of the tissue mucopolysaccharides rather than an increase in the total concentration of these compounds may be responsible for the increased metachromasia reported in arteriosclerosis.

## SUMMARY

Determinations were made of the concentrations of hexosamine and acid-hydrolyzable sulfate in a large group of aortic and pulmonary artery samples obtained from individuals ranging in age between 5 weeks and 89 years. The hexosamine analyses were performed by Boas' modification of Elson and Morgan's method and the sulfate determinations by a modification of Hoagland's procedure developed by the authors.

The average concentrations of hexosamine (N=113) and acid-hydrolyzable sulfate (N=101) found in the wet aortic tissue, were respectively, 0.30 per cent (s.d. of distribution, 0.067) and 0.075 per cent (s.d. of distribution, 0.023). No significant change in the tissue content of these compounds with age was observed.

For the pulmonary artery samples the mean hexosamine (N=85) value found was 0.27 per cent (s.d. of distribution, 0.052) and the mean acid-hydrolyzable sulfate concentration (N=68) 0.070 per cent (s.d. of distribution, 0.021) expressed on the basis of wet tissue weight. No significant change in the hexosamine concentration was noted with age, whereas the acid-hydrolyzable sulfate values were found to be higher for individuals aged 50-79 years than for younger subjects.

A calculation was made of the tissue concentration of non-chondroitin sulfate hexosamine. An average value of 0.160 per cent was found for the aortic samples, and a mean value of 0.135 per cent for the pulmonary artery samples (calculated on the basis of wet tissue weight). These concentrations are, respectively, 54 and 50 per cent of the total hexosamine values found.

No significant correlation was observed between the cholesterol content of the tissue and the hexosamine and sulfate concentrations for aortic and pulmonary artery samples from individuals aged 55-89 years.

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# SOME BIOCHEMICAL ASPECTS OF AGING IN INSECTS*

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For the last decade or so gerontologists (9) have emphasized the strong need for more research on the basic mechanisms of the aging process.

Lansing's (8) already classical study of aging in rotifers is testimony to the advantages and possibilities of studying in lower animals this universal property of all animals. These include their relatively short life spans, ease of keeping and rearing, and availability in large numbers, all of which make them admirably suitable for extended aging studies, during the relatively limited life span of the investigator himself. One can, for example, keep 75,000-100,000 bees (and at considerably lower cost) in the space which would not accommodate more than 50 rats comfortably; in the same space over a half million house flies can be adequately maintained. Yet, their size is not so small as to render insects incapable of manipulation and even of being operated upon, after a little practice. For aging studies, insects with an average longevity of several weeks to several months permit replication of several complete studies from emergence to senility in one year. The tremendous reproductive potential, coupled with this short life span means the availability of large numbers of individuals of the same age from one parent in one day, as well as the possibility of building up a relatively pure strain within a comparatively short period of time. From a single queen bee fertilized by a single drone, for example, one can obtain 2,000-3,000 adult worker bees in one day, and up to a total of 100,000 during her lifetime.

The statement by Sumner (19) that "life is an orderly functioning of enzymes" can be broadened to suggest that disease or even senility should have an internal reflection of disorder or imbalance of the enzyme activity for the tissue(s) or organ(s) involved. From that point of view, the present writer embarked on a long-term study of the aging process in terms of changes in enzyme activity as a function of age, earlier in the honey bee and more recently in the house fly. Such studies, it is hoped, will not only add to the general understanding of the aging process, but also provide a pattern for similar studies in mammals, including man.

Initially a study was undertaken with worker honey bees to determine what changes occur in brain cell number with advancing age. Concomitantly, estimation was made of the possible alterations with age in activity of the enzyme cholinesterase, important in the hydrolysis of acetyl choline (recognized by most physiologists as the chemical mediator of the nerve impulse at certain synaptic junctions and at the myoneural junction in skeletal muscle). Just as in the case of brain and spinal ganglionic cells of humans and rats (1, 2, 3, 4, 5, 6, 7), the brain cells of the honey bee were observed to decline gradually in number with age to about 65 per cent of the original number in very old bees 65-75 days of age (14, 15). This was true both for marked bees in the normal hive environment as well as for substantially large numbers of worker bees maintained in large cages without queen or brood to rear. Interestingly enough, total brain cholinesterase activity was found to rise steadily during the first week to 10 days of adult life, after which no further change was observed. From studies on changes in brain cholinesterase in guinea pigs (physically well developed at birth) and in rats and rabbits (with poorly developed motor ability at birth), Nachmansohn (11, 12, 13) has suggested that maturation of the neuromotor function in these animals is reflected in the level of activity of cholinesterase. Inasmuch as flight activities of the adult worker honey bee are not initiated until the worker is about a week or more old, it seems that this change in cholinesterase activity during the corresponding period of adult life must be associated with maturation of the neuromotor activities concerned with flight. It is of further interest that this cholinesterase level is maintained unchanged

Submitted for publication February 1, 1956.

* Part of this investigation was supported by the Research and Development Division, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-499.

This paper is based in part on a report delivered before the Section on Biological Sciences at the Eighth Annual Scientific Meeting of the Gerontological Society, October 27-29, 1955, Baltimore.

even in brains of very old bees, just as senescent bees are capable of competent flight even in quite old age.

In further pursuance of the original objectives of this study, the activities of acid and alkaline sodium beta-glycerophosphatase were measured in total homogenates of honey bees from emergence to senility. These enzymes, readily measurable, are especially important in a number of intermediary metabolic processes involving protein and carbohydrates, (10). The acid enzyme showed an increase of 90 per cent by the end of the first week of adult life, with the alkaline phosphatase showing a reciprocal decline during the same period. Both levels observed remained unchanged through old age. As in the case of brain cholinesterase, it seems that such changes are related to the maturation of biochemical mechanisms associated with developing flight ability of the young worker bee and that the phosphomonoesterases studied are not involved in senescence of this species (16).

However, in a recent study concerned with certain aspects of phosphorus metabolism in adult house flies, some interesting data were obtained which warranted further study of the changes in such metabolism in aging male house flies. This consisted of the determination of changes in activity with age of acid sodium beta-glycerophosphatase and (more recently) of magnesium-activated adenosine triphosphatase for flies reared and maintained under conditions of constant temperature, humidity, food, and handling.

## METHODS

Flies were reared from pupae of long-inbred NAIDM house flies *(Musca domestica)*† and were maintained in an air conditioned room, at 80 F. and 40 per cent relative humidity. Emerging flies were isolated in a large number of individual cages and supplied with sugar and water. At stated intervals (see below) all living flies were collected and inactivated by rapid freezing at −25 C. Twenty males were homogenized for 3 minutes with 1 ml. of ice-cold deionized water, in a Potter-Elvehjem homogenizer in an ice-bath. After filtration under suction through a uniform glass wool disk of constant thickness of 25 mm. diameter and 60 mg. weight, the homogenate was diluted to a 10 ml. total volume with cold deionized water. The acid phosphatase activity was determined with the following mixture:

Acid Phosphatase
(pH 5.4)

1) 1 ml. diluted homogenate
2) 0.5 ml. 0.8M $MgCl_2$
3) 0.6 ml. 0.33 N Acetic Acid
4) 0.4 ml. 1 M $Na_2$ beta-glycerophosphate dissolved in 0.848 per cent sodium diethyl barbiturate

All procedures carried out prior to incubation employed reagents maintained at zero to 5 degrees C. A drop of chloroform was added to each incubation mixture and the container vials stoppered tightly and inverted to mix thoroughly and quickly transferred to a constant temperature bath maintained at 35 C. After a 5-minute wait to allow for temperature equilibration, incubation was permitted for 25 minutes. Controls were treated exactly like experimental tubes, except that they were inactivated immediately after the 5-minute warm-up period, the end of which was established as zero time. Inactivation (and deproteinization) was effected by rapid addition of 0.2 ml. of 30 per cent trichloroacetic acid to 1.0 ml. samples of the incubation mixture. After filtration through Whatman 42 filter paper, inorganic phosphate content of 0.2 ml. samples of this deproteinized mixture was estimated by the acid molybdate-ferrous sulfate colorimetric method described previously (17). Final activity was calculated from the net absorbance (*i.e.*, experimental minus control) values obtained, in relation to standard phosphate samples. Activity is expressed as micrograms of phosphorus released per 25 minutes for 0.2 ml. of deproteinized incubation mixture. (To convert to activity per milliliter of diluted homogenate representing 2 flies, the data given are multiplied by a factor of 15).

## RESULTS

Table 1 summarizes the data for acid phosphatase activity for 3 series of flies, the first 2 representing flies from one source and the third flies from another laboratory. A minimum of 4 experimental and 4 control determinations were made for each age group of each series. The combined mean data for series 1 and 2 usually refer to the average of 2 such sets of determinations per age group. It appears from these results that the acid enzyme declines steadily to a minimum some time after the tenth day of

† Kindly supplied by Dr. Albert S. Perry of the U.S.P.H.S. Technical Development Laboratories at Savannah, Georgia.

TABLE 1. ENZYME ACTIVITY* AND AGE (ADULT MALE HOUSE FLIES (*Musca domestica*))

| Series 1 and 2 | | Series 3 | |
|---|---|---|---|
| Age | Acid Phosphatase | Age | Acid Phosphatase |
| 4 hrs. | 5.6 | 24 hrs. | 3.6 |
| 8 hrs. | 5.1 | 48 hrs. | 2.2 |
| 24 hrs. | 4.8 | 4 days | 1.8 |
| 48 hrs. | 4.1 | 6 days | 1.8 |
| 4 days | 2.3 | 8 days | 1.5 |
| 7 days | 2.1 | 11 days | 1.1 |
| 11 days | 1.8 | 13 days | 1.2 |
| 14 days | 1.8 | 15 days | 1.0 |
| 21 days | 1.7 | 18 days | 1.1 |

* Micrograms of P released/25 min./0.2 ml. deproteinized mixture.

adult life in the male house fly. Recalculation of the above data on an activity per milligram nitrogen basis (from microkjeldahl estimations of N in aliquots of the homogenates) gives the same observed trend. Preliminary data on the corresponding changes in magnesium-activated adenosine triphosphatase with aliquots of the homogenates employed earlier for acid phosphatase show a similar trend.

During the collecting of male house flies at various ages, it was noted that the number of males surviving in any cage decreased with time at a greater rate than the females. Furthermore, under the conditions of maintenance of these flies, by the end of the twelfth to fourteenth day, the wings of most male house flies were noticeably abraded, and the males reduced to walking or creeping about the cage. The females not only persisted in proportionately larger numbers but even at the end of 3 weeks most of the females retained their flight ability. To test the above observations actual counts were made of surviving members of each sex for flies corresponding to those used in series 3 of table 1, as follows: Five groups of about 100-150 flies each were allowed to emerge into separate screen cages containing ample supplies of sugar and water. At each particular age indicated below, the total number of living males and females was determined for one of the cages (taken at random) and the cage and its flies were then discarded. In the case of 24-hour old flies, with no deaths, the counts were taken for two cages. The following results were obtained:

| Age | 24 hours (I) | 24 hours (II) | 13 days | 19 days | 21 days |
|---|---|---|---|---|---|
| Females | 67 | 68 | 57 | 103 | 136 |
| Males | 35 | 79 | 30 | 20 | None |

Although the original male : female ratio was 1 : 1, this ratio is seen to fall, even from the few data shown. This suggests that the male house fly has a considerably shorter longevity than the female.

## DISCUSSION

Although many papers have been written concerning the biochemical activities and histochemical changes in acid and alkaline phosphatase, as Moog (10) has pointed out, the function of these enzymes is not precisely known for most tissues. However, one important function in the complex glycolytic intermediary metabolic processes has been stressed by a number of biochemists including Meyerhof (18), *viz.*, that alkaline and acid phosphatases are involved in important transphosphorylative processes. Adenosine triphosphatase more specifically is recognized as important in a number of specific biologic phenomena (choline acetylation, bioluminescence, and muscle contraction) through dismutation of the high-energy labile phosphate bonds of ATP by which important substrates are activated through their corresponding enzymes (choline acetylase, luciferinase, and hexokinase).

Most probably the primary importance of phosphorus metabolism in living cells is the formation with organic constituents (of such cells) of important intermediary compounds in the complex metabolism ultimately concerned with the release of energy. It is not unreasonable, therefore, on the basis of observations, reported in the present paper, to envision senescence of flight ability of this species as outwardly reflecting a decline at the cellular level of catalysts important in the normal metabolism of phosphorus compounds. Just as an earlier study (15) showed that the maturation of the function of flight is accompanied by an increase in acid phosphatase (and brain cholinesterase) activity in the developing young honey bee, decline of this function in the house fly is conversely accompanied by a fall in activity of acid phosphatase and of adenosine triphosphatase. In this connection, Williams, Barness, and Sawyer (21) found that glycogen content as well as flight ability (as measured by wing-beat frequency and duration of flight) both decline in parallel fashion to a minimum at 24 days of age in *Drosophila funebris*. Like the data presented in the present paper, the authors have observed a distinctly positive correlation be-

tween an observable, outward manifestation of senescence and measurable biochemical alterations with advancing age. More recently, Watanabe and Williams (20), in a study of the biochemistry of the giant mitochondria of flight muscle of the blow fly, observed that catalase activity declines slowly with age. Finally, the observations reported upon by the present writer suggest a similar plan of attack on aging in mammals (like man and the albino rat), in which species old age is accompanied by gradual decline in total skeletal muscle mass and vigor, and even by "muscular dystrophy" in senile rats. A study of the changes in enzyme and substrate concentrations concerned in phosphorus metabolism in the skeletal muscles of aging rats is being initiated by the present writer.

## SUMMARY

Unlike the worker honey bee in which flight ability and phosphorus metabolism remain at a high level until very old age, adult male house flies *(Musca domestica)* lose the power of flight by the end of the second week of adult life. Outward signs of senescence include an abraded, worn appearance to the wings. Concomitantly, activities of acid sodium beta-glycerophosphatase and magnesium-activated adenosine triphosphatase of total fly homogenates decline gradually with age to a minimum by the eleventh day of adult life. These biochemical changes suggest a degenerative alteration in phosphorus metabolism at the cellular level, which outwardly is reflected by declining flight ability in the male house fly.

Males (from a long-inbred strain of normal house flies, maintained under conditions of constant temperature, humidity, food, and handling) show a consistently shorter average longevity (less than 21 days) than females.

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# NEUROHYPOPHYSEAL RESPONSIVENESS IN THE NORMAL AND SENESCENT RAT*

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Recently, in a study of salt and water metabolism (2), evidence suggesting a decline in neurohypophyseal function in senescent rats was presented. Later (3), it was observed that Pitressin exerts a direct effect on the movement of water into cells. This again suggested that the progressive shift of water to the extracellular phase in the later decades of life (4) might result in part from a failure in neurohypophyseal function. It is of interest that Findley (1), integrating clinical and some experimental data, suggested that failing function in the posterior lobe of the pituitary is important in the aging process.

In a series of experiments, Verney (5) has demonstrated the release of antidiuretic hormone by an appropriate osmotic stimulus to the pituitary gland in the dog. It seemed that the principle of applying an osmotic stimulus might readily be adapted as the basis of a method for studying the stimulability of the neurohypophysis directly under various experimental conditions. This report presents proof for the validity of the method as finally evolved for the rat and direct evidence for a decline in neurohypophyseal function with age in this species.

## METHODS

Adult albino rats of an inbred Wistar strain were used throughout. Polyethylene tubing (O.D., 0.038 inches) was prepared by filling a 3 inch length with isotonic saline and stopping one end with a glass rod obturator. Under ether anesthesia, the right common carotid artery was cannulated with this tube and the wound closed. The tube was carried down under the right axilla and then, with stay sutures, carried up along the back of the neck.

One hour was allowed for recovery from the operation and anesthetic; the remainder of the procedure was carried out in the unanesthetized animal. The bladder was emptied by gentle suprapubic pressure and 3 ml. of distilled water given by stomach tube. Urine was collected between 30 and 60 minutes after gavage. Immediately following this, an intracarotid infusion was administered in the 61st minute by injection into the tubing. The tube was then clamped beyond the puncture site, the punctured section cut away, the tubing re-stopped, and the clamp removed. The entire procedure for intracarotid injection was easily completed within one minute with gentle handling of the unanesthetized animal.

Following the intracarotid injection, urine was collected for two 15 minute periods and then for two further 30 minute periods. The rates of water excretion during the 2½ hours following gavage could thus be calculated. The choice of time for intracarotid injection (60 minutes after gavage) was based on preliminary studies which showed that this time preceded the peak of the diuretic response to the water load.

The data were studied by two simple methods. For the first, the average rates of urine excretion in the groups being compared were plotted and the range of variation at the critical periods, i.e., before and after intracarotid injection, was calculated. For the second, a quantitative assessment of the effect of the injection, the rate of urine flow after injection ($R_2$) was related as a change from the rate before injection ($R_2—R_1$). This difference was then expressed as a percentage change in slope, i.e., $\frac{R_2—R_1}{R_1} \times 100$. Positive values occur when the rate of urine flow increases, negative values when it decreases after injection. The standard error of the mean of these data was calculated using the formula $\frac{\sqrt{\Sigma d^2}}{\sqrt{n\,(n-1)}}$. It is thus quite simple to distinguish positive from negative pituitary responses with this procedure.

Submitted for publication February 7, 1956.

* This work was carried out with the aid of a grant from the National Research Council of Canada.

## EXPERIMENTAL

*Experiment I. The Effect of Variation in the Osmotic Strength of the Stimulating Solution.*—Three separate experiments were carried out. In each, the control group received 0.25 ml. of 0.8 per cent NaCl by injection into the carotid cannula. In Experiment IA the test group received an intracarotid injection of 0.25 ml. of 2 per cent NaCl as stimulant. In Experiment IB the stimulant was 0.25 ml. of 1.5 per cent NaCl and in Experiment IC it was 1.2 per cent NaCl. In each case the control and test group were closely matched in weight. The data are presented in table 1 and in figure 1.

Clearly, a marked antidiuretic response followed the intracarotid injection of 2 per cent and 1.5 per cent NaCl. The diuresis curve was undisturbed by 1.2 per cent NaCl.

TABLE 1. THE ANTIDIURETIC EFFECT OF INTRACAROTID INJECTION OF NaCl SOLUTIONS OF VARYING STRENGTHS. THE INJECTION, IN A VOLUME OF 0.25 ML., WAS GIVEN IN THE 61ST MINUTE. $R_1$ = RATE OF URINE FLOW BEFORE INJECTION; $R_2$ = RATE OF URINE FLOW AFTER INJECTION.

| | Experiment IA | | Experiment IB | | Experiment IC | |
|---|---|---|---|---|---|---|
| Treatment | 0.8% NaCl | 2% NaCl | 0.8% NaCl | 1.5% NaCl | 0.8% NaCl | 1.2% NaCl |
| No. of animals | 7 | 7 | 6 | 5 | 6 | 6 |
| Average weight (Gm.) | 181± 6 | 184± 3 | 157± 8 | 166± 7 | 167±10 | 183±10 |
| Urine excretion [μl/min. | | | | | | |
| 30-60 mins. ($R_1$) | 36± 8 | 31± 5 | 41± 5 | 48± 7 | 47±10 | 50±13 |
| 60-75 mins. ($R_2$) | 43± 8 | 10± 4 | 60±12 | 23± 6 | 47± 9 | 53±12 |
| 75-90 mins. | 40± 7 | 16± 5 | 38±11 | 16± 4 | 30± 6 | 46±18 |
| $\frac{R_2-R_1}{R_1} \times 100$ | +24±21 | −74±11 | +91±45 | −52±11 | +28±27 | + 5±20 |
| | p<0.01 | | p<0.01 | | | |

*Experiment II. Sex as a Variable in the Antidiuretic Response to an Intracarotid Osmotic Stimulus.*—Six male and 6 female rats, matched in weight at approximately 175 Gm., were prepared for intracarotid injection. All the animals received 0.25 ml. of 1.5 per cent NaCl as intracarotid stimulant. The findings for the surviving animals are presented in table 2 and figure 2.

An antidiuretic effect was obtained with this stimulus in both groups. There is a suggestion that the response was greater in the females

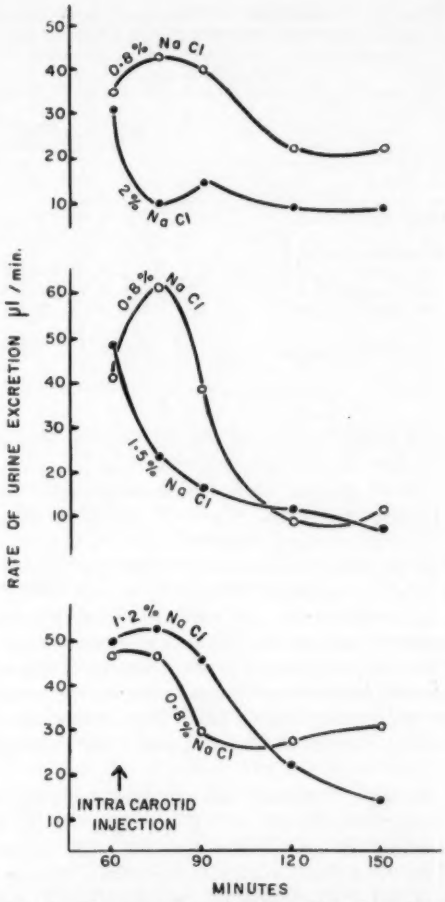


Fig. 1. The average antidiuretic effect of an intracarotid injection of 0.25 ml. of 2% and of 1.5% NaCl in young male rats. The injection was carried out in the 61st minute, immediately after the first urine collection.

but much larger groups would be needed to investigate this point. Our main concern with these findings was in the demonstration that the antidiuretic response could be elicited at least as readily in the female as in the male.

*Experiment III. Body Weight as a Variable in the Antidiuretic Response to an Intracarotid Osmotic Stimulus.*—In preliminary studies we noted that a larger volume of the intracarotid stimulant was required to elicit a sharp antidiuresis in larger animals. The present experiment was designed to demonstrate this effect of body weight. It was also intended to serve

TABLE 2. A COMPARISON IN MALE AND FEMALE RATS OF THE ANTIDIURETIC RESPONSE TO THE INTRACAROTID INJECTION OF A NaCl SOLUTION OF STANDARD (1.5%) STRENGTH.

| Group | Male 1.5% NaCl | Female 1.5% NaCl |
|---|---|---|
| No. of animals | 4 | 5 |
| Average weight (Gm.) | 171 ± 8 | 178 ± 5 |
| Urine excretion, λl/min. | | |
| 30 – 60 mins. ($R_1$) | 43 ± 10 | 55 ± 7 |
| 60 – 75 mins. ($R_2$) | 30 ± 7 | 32 ± 2 |
| 75 – 90 mins. | 28 ± 12 | 20 ± 5 |
| $\frac{R_2 - R_1}{R_1} \times 100$ | −27 ± 3 | −40 ± 8 |

as a general guide for the selection of dosages for other studies in larger rats.

Three groups of 6 female rats each were selected from stock. Group 1, which served as reference standard, weighed 140-190 Gm. as in the preceding experiments. The test Groups, 2 and 3, weighed 230-250 Gm. and 280-350 Gm., respectively, and were thus broadly separated in weight but not in age (4-6 months). The volume of water given to ensure a diuresis was adjusted for weight according to the results of preliminary trials. Thus, 3 ml. was given to Group 1, 4 ml. to Group 2, and 5 ml. to Group 3.

Group 1 received the standard intracarotid injection (0.25 ml. of 1.5 per cent NaCl) to provide, as previously demonstrated, control data for a positive antidiuretic effect. Group 2 received 0.35 ml. of 1.5 per cent NaCl, con-

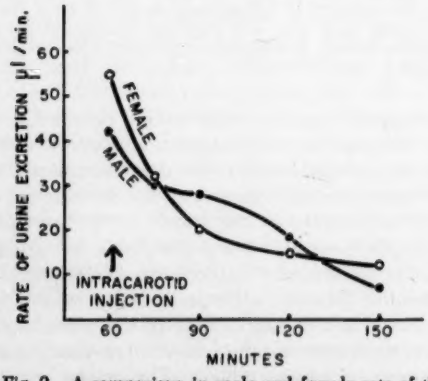


Fig. 2. A comparison in male and female rats of the average antidiuretic effect of an intracarotid injection of 0.25 ml. of 1.5% NaCl.

TABLE 3. THE EFFECT OF BODY WEIGHT ON THE VOLUME OF INTRACAROTID NaCl INJECTION OF STANDARD (1.5%) CONCENTRATION REQUIRED TO PRODUCE AN ANTIDIURETIC EFFECT.

| Group | Weight Range 140–190 Gm. | Weight Range 230–250 Gm. | Weight Range 280–350 Gm. |
|---|---|---|---|
| No. of animals | 4 | 6 | 4 |
| Volume of intracarotid injection | 0.25 ml. | 0.35 ml. | 0.35 ml. |
| Concentration of intracarotid injection | 1.5% | 1.5% | 1.5% |
| Average weight, (Gm.) | 165 ± 9 | 236 ± 2 | 305 ± 10 |
| Urine excretion, λl/min. | | | |
| 30 – 60 mins. ($R_1$) | 57 ± 12 | 53 ± 10 | 49 ± 9 |
| 60 – 75 mins. ($R_2$) | 29 ± 12 | 23 ± 6 | 54 ± 11 |
| 75 – 90 mins. | 12 ± 5 | 10 ± 3 | 21 ± 5 |
| $\frac{R_2 - R_1}{R_1} \times 100$ | −53 ± 15 | −57 ± 7 | +45 ± 10 |
| | | $p<0.01$ | |

sidered a positive stimulus from preliminary trials for this weight range. Group 3, the unknown test group, received the same treatment as Group 2. Thus, in this experiment, Groups 2 and 3, differing only in weight, were to be compared with one another against the background of a known control positive result in Group 1. The results in the surviving animals are presented in table 3 and in figure 3. A positive antidiuretic effect was obtained, as ex-

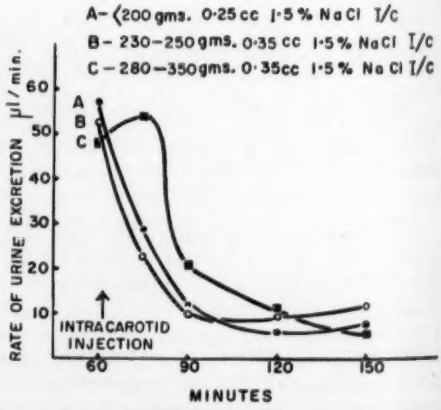


Fig. 3. The effect of body weight on the volume of intracarotid NaCl injection of standard (1.5%) concentration required to produce an antidiuretic effect. A positive response was obtained in A and B, while the stimulus was inadequate in C.

pected, in both Groups 1 and 2. In Group 3, the volume of the stimulus was inadequate to influence the course of diuresis.

*Experiment IV. The Specificity of the Intracarotid Route of Injection.*—This experiment was designed to demonstrate that the amount of NaCl injected is in itself inadequate to provoke an antidiuretic effect through any general effect on salt concentration. Two groups of 6 female rats each, approximately 250 Gm. in weight, were selected from stock. Both groups were handled identically except for the fact that in Group 1 the polyethylene tubing was implanted into the right femoral artery instead of into the right common carotid artery as in Group 2. The stimulus used in both cases was 0.35 ml. of 1.5 per cent NaCl as demonstrated for this weight range in the previous experiment. The results in the surviving animals are presented in figure 4 and in table 4.

The average rate of urine excretion before the injection of NaCl was higher in Group 1. This chance occurrence placed the curves for the two groups at different levels. The response of the two groups to injection at the two sites was, however, sharply and obviously different. Thus, injection into the femoral artery in no way affected the normal diuresis curve, while the usual antidiuretic response followed the intracarotid injection.

*Experiment V. The Dependence of Antidiuretic Response to an Intracarotid Osmotic Stimulus on the Presence of an Intact Pituitary Gland.*—Although Verney had clearly implicated the pituitary in the response to an intracarotid osmotic stimulus in the dog, proof was required that this was also true in the present procedure in the rat.

TABLE 4. THE SPECIFICITY OF THE INTRACAROTID ROUTE OF INJECTION IN ELICITING AN ANTIDIURETIC RESPONSE TO A NaCl SOLUTION OF STANDARD (1.5%) STRENGTH.

| Group | Femoral Artery Injection 1.5% NaCl | Carotid Artery Injection 1.5% NaCl |
|---|---|---|
| No. of animals | 6 | 5 |
| Average Weight, (Gm.) | 244 ± 12 | 267 ± 14 |
| Urine excretion, $\mu$l/min. | | |
| 30 – 60 mins. ($R_1$) | 58 ± 8 | 34 ± 5 |
| 60 – 75 mins. ($R_2$) | 70 ± 16 | 12 ± 7 |
| 75 – 90 mins. | 64 ± 10 | 23 ± 12 |
| $\frac{R_2 - R_1}{R_1} \times 100$ | +12 ± 13 | −68 ± 17 |
| | p<0.01 | |

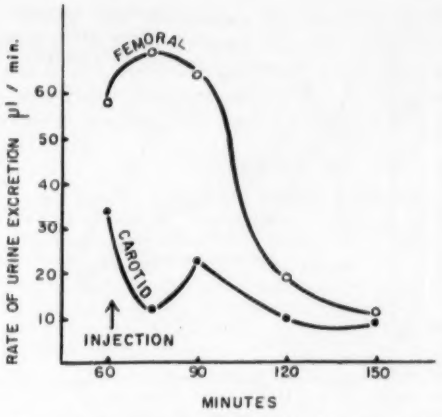


Fig. 4. The average antidiuretic response obtained with 0.35 ml. of 1.5% NaCl injected into the carotid artery in one group of rats in contrast with the absence of response on injection of the same solution into the femoral artery.

Six adult female hypophysectomized rats were obtained from a commercial supplier together with 6 matched controls of the same strain and age. The hypophysectomized animals were maintained on cortisone acetate (2 mg./day for 8 days) as a preparatory aid against the trauma of the operative part of the test procedure. To ensure good urine flows in the test, the drinking water of both the hypophysectomized and control groups during the preliminary 8 days contained 1 per cent NaCl and 5 per cent dextrose. As a result of these precautions, a satisfactory diuresis was obtained in the final test in 3 rats. To ensure a certainly adequate intracarotid stimulation the very large volume of 0.45 ml. of 1.5 per cent NaCl was used in both groups. Figure 5 presents the results obtained in the individual hypophysectomized rats in comparison with the average curve of the control group. Although only 3 hypophysectomized animals survived this procedure, they seem adequate to indicate that no antidiuretic response occurs in the absence of the pituitary.

*Experiment VI. The Stimulability of the Neurohypophysis in Age.*—The preceding experiments had demonstrated the specificity of the test procedure. In this experiment, the test procedure was applied in a comparison of the

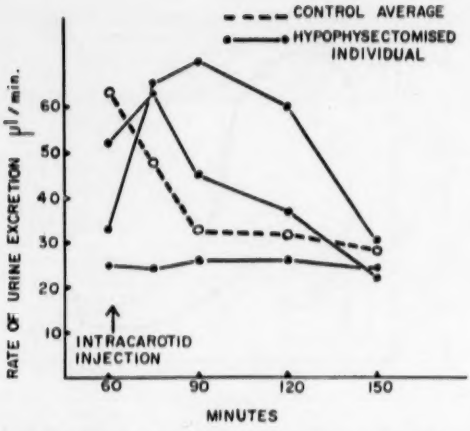


Fig. 5. The failure of a strong intracarotid stimulus, 0.45 ml. of 1.5% NaCl, to produce any antidiuresis in 3 hypophysectomized rats (plotted individually in contrast with the average response obtained in the control group).

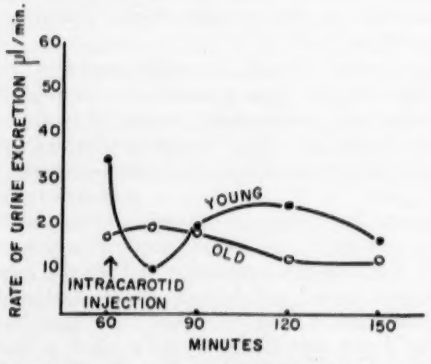


Fig. 6. The average antidiuretic response of a group of young rats contrasted with the failure of a matched group of old rats to respond to the same stimulus.

response of young and old rats of approximately the same weight to the same neurohypophyseal stimulus.

Since the selection for age was based on simple chronology, considerable variability was expected. Accordingly, large groups of rats were used. Group 1 consisted of 12 young females less than 6 months in age and of an average weight of 217 Gm. Group 2 consisted of 13 old females not less than 20 months old and of an average weight of 255 Gm. Both groups were treated identically. In all cases, 1.5 per cent NaCl was used as stimulus. The volume

TABLE 5. THE EFFECT OF AGE ON THE ANTIDIURETIC RESPONSE TO THE INTRACAROTID INJECTION OF A NaCl SOLUTION OF STANDARD (1.5%) STRENGTH.

| Group | Young 1.5% NaCl | Old 1.5% NaCl |
|---|---|---|
| No. of animals | 12 | 13 |
| Average weight, (Gm.) | 217 ± 8 | 255 ± 9 |
| Urine excretion, [µl/min. | | |
| 30 – 60 mins. ($R_1$) | 34 ± 7 | 17 ± 5 |
| 60 – 75 mins. ($R_2$) | 10 ± 2 | 19 ± 4 |
| 75 – 90 mins. | 19 ± 3 | 18 ± 4 |
| $\frac{R_2 - R_1}{R_1} \times 100$ | −47 ± 19 | +47 ± 29 |
| | $p<0.01$ | |

injected was adjusted in accordance with the findings of Experiment 3; rats weighing less than 200 Gm. receiving 0.25 ml., those between 200 and 300 Gm., 0.35 ml. No rats exceeded 300 Gm. and only 2 control rats weighed less than 200 Gm. Because of the large size of the rats, 4 ml. was chosen as the volume of distilled water to be given by stomach tube to all experimental animals. The observations are presented in table 5 and in figure 6.

The stimulus that elicited a clear-cut antidiuretic response in the young rats failed completely to do so in the older animals. This result was demonstrable both in the shapes of the curves as well as in the calculation of the change of rate following intracarotid injection.

## DISCUSSION

These experiments demonstrate that the pituitary gland of the rat responds to an appropriate osmotic stimulus by the release of antidiuretic material. The procedure is less precise than that used by Verney in the dog, but permits useful group comparisons.

In these experiments, we have not attempted to measure the degree of response but have restricted our observations to simple positive and negative antidiuretic effects. The data, however, provide some suggestion of a graded pituitary response. Thus, frequently a rapid rebound in the rate of excretion was observed to follow the initial antidiuretic response. Presumably, no such rebound occurred when the response was greater in degree. The procedure might be refined to give more detailed information.

The method was devised with the primary

aim of securing information concerning neurohypophyseal function in certain specific states and, in particular, in senescence. In previous studies (2), we had noted that old normotensive rats given a hypertonic salt load responded with a greater than normal loss of water. This effect was not due to a diminished responsiveness to Pitressin nor to any apparent renal fault, which suggested the alternate possibility that the neurohypophysis in these old rats was less responsive than in the younger animal. The present direct experiments bear this out. Further work will aim at an exploration of the relation of this diminution in neurohypophyseal function to the general processes of senescence.

## SUMMARY

A method is described for the direct stimulation of the neurohypophysis in the unanesthetized rat by the intracarotid injection of an appropriate solution of sodium chloride. Evidence is presented to demonstrate the specificity of the test.

Using this procedure, the response of the neurohypophysis in aged rats was tested and was found to be refractory to direct stimulation. This is interpreted as evidence for a decline in neurohypophyseal function in age.

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# OBSERVATIONS ON BLOOD VESSELS AND EXERCISE*

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The long term effect of a moderately vigorous existence as compared to a sedentary life on the development of atherosclerotic coronary heart disease has interested physicians for many years. Recently the effect of physical work on the development of coronary heart disease in humans has been studied from the epidemiologic standpoint with some fruitful results. Morris and associates (3) from the Social Medicine Research Unit have been engaged in a survey of the health records and death certificates of some 31,000 men from 35 to 64 years of age employed in the London Transport System. Conductors on trains and busses were selected to represent the active occupation group because their jobs entailed either walking or climbing, whereas the drivers of these vehicles because they sat at their work were chosen to represent the sedentary group. Notations were made of the incidence of angina, coronary occlusion, and early mortality from myocardial infarction in the two classes of workmen. Their survey showed a greater incidence of coronary artery disease as well as a greater immediate mortality from coronary artery disease in the driver (sedentary) than in the conductor (active) groups. As a further test of the incidence of coronary disease in two comparable classes of workers the medical records of over 100,000 male postal workers and civil servants were reviewed. Postmen who delivered mail represented the actively exercising group while supervisors, telegraph, and telephone operators comprised the sedentary group. As above, the total incidence of coronary disease was significantly less in the men whose work involved exercise.

In attempting to evaluate the effect of the exercise factor in the prevention of coronary disease several points must be kept in mind. The complexity of everyday living in humans is so great that it is difficult to resolve other possible etiologic factors such as diet, mental strain, heredity, and rest and to evaluate their separate or combined effects on the development of arteriosclerosis in general and coronary disease in particular. The problem of coronary disease is still further complicated by the subsequent morbid processes which follow coronary atherosis such as thrombosis, intramural hemorrhages into atheromata, and the anatomic location of the atheroma which may determine the difference between life and death.

In an attempt to simplify the problem somewhat it was thought worth while to test the efficacy of exercise in preventing coronary atherosclerosis in rabbits on a cholesterol atherogenic diet. We realized that this method may well have little application to the problem in humans particularly since rabbits absorb cholesterol very readily and seem to have great difficulty in metabolizing or excreting it. It was thought, however, that the effect of exercise in preventing the development of coronary atherosclerosis in rabbits on a cholesterol diet should at least receive a preliminary test.

## MATERIAL AND METHODS

Eighty-four Weanling Silver Martin rabbits of 4-5 weeks of age were placed on a basal diet of commercial rabbit pellets. Four animals died during the experiments (table 1). Food and water were fed ad libitum, but feed intake was recorded for each animal. In the cholesterol-fed groups of animals cholesterol in ether was coated on the pellets so as to provide two concentrations, one to make the concentration 0.1 per cent by weight, and the other 0.5 per cent by weight of the dry feed. In the exercise groups, compulsory exercise was given each day in a cylindrical barrel which was attached to a motor and run horizontally 12-15 rounds per minute (fig. 1).

The over-all investigation was designed as shown in table 1. Two dosage levels of cholesterol were employed in order to produce a borderline and an advanced degree of atherosis in a dosage period of 6-12 weeks. At the 0.1 per cent level of cholesterol intake, lesions rarely developed at 6 weeks, and minimal to moderate atherosis appeared in half the animals in 12

Submitted for publication December 14, 1955.

* The work performed at Cornell was supported by a research grant of the United States Public Health Service, No. H-1658, National Heart Institute, Bethesda, Maryland.

The Lankenau Hospital research was supported by a grant from Mr. John A. Diemand, President, Insurance Company of North America.

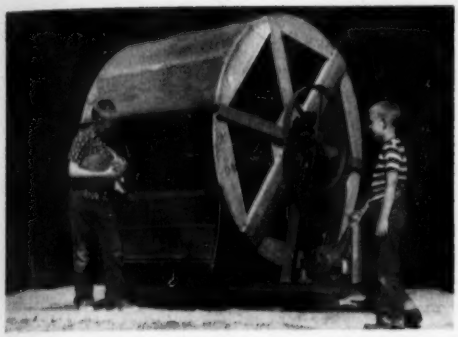

Fig. 1. Rabbit Exerciser as developed by C. M. McCay for studies on exercise tests for lower animals. Note it is portable and relatively light in weight. The large screened-in cylinder is turned via a belt attached to a small electrically powered motor.

TABLE 1. EXERCISE, CHOLESTEROL, AND ATHEROSIS.

| Group No. | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Cholesterol added, % of diet | 0 | 0 | 0.1 | 0.1 | 0.5 | 0.5 |
| **Experiment Number I** | | | | | | |
| Daily exercise (mins.) | 0 | 20 | 0 | 20 | 0 | 20 |
| Expt. ran (weeks) | 6-8-12 | 6-8-12 | 6-8-12 | 6-8-12 | 6-8-12 | 6-8-12 |
| Number animals | 1-2-2 | 2-2-2 | 2-2-2 | 2-2-2 | 2-2-2 | 2-2-2 |
| Atherosis (degree) | | | | | | |
| Aorta | 0-0-0 | 0-0-0 | 0-1-2 | 0-2-2 | 2-3-3 | 2-3-3 |
| Coronary | 0-0-0 | 0-0-0 | 0-1-1 | 0-0-1 | 2-3-2 | 2-3-2 |
| Adrenal | 0-0-0 | 0-0-0 | 1-1-2 | 1-2-2 | 2-3-3 | 3-3-3 |
| **Experiment Number II** | | | | | | |
| Daily exercise (mins.) | | 0 | 20 | 0 | 20 | |
| Expt. ran (weeks) | | 12-12 | 12-12 | 12-12 | 12-12 | |
| Recovery (weeks) | | 4-10 | 4-10 | 4-10 | 4-10 | |
| Number animals | | 2-1 | 2-2 | 2-2 | 2-2 | |
| Atherosis (degree) | | | | | | |
| Aorta | | 1-0 | 0-1 | 3-3 | 3-3 | |
| Coronary | | 1-0 | 0-2 | 3-2 | 3-2 | |
| Adrenal | | 1-0 | 0-2 | 3-3 | 3-3 | |
| **Experiment Number III** | | | | | | |
| Daily exercise (mins.) | | 0 | 60 | 0 | 60 | |
| Expt. ran (weeks) | | 12-12 | 12-12 | 12-12 | 12-12 | |
| Recovery (weeks) | | 4-8 | 4-8 | 4-8 | 4-8 | |
| Daily exercise during recovery (mins.) | | 0-0 | 60-60 | 0-0 | 60-60 | |
| Number animals | | 4-4 | 3-4 | 4-4 | 3-4 | |
| Atherosis (degree) | | | | | | |
| Aorta | | 1-1 | 1-1 | 3-3 | 3-3 | |
| Coronary | | 0-0 | 0-0 | 2-3 | 3-3 | |
| Adrenal | | 1-2 | 1-1 | 3-3 | 3-3 | |

weeks. Thus exercise effects might be discernible earlier in this group than with the more or less overwhelming degree of atherosis that resulted from the 0.5 per cent cholesterol dosage. In Experiments I and II 20 minutes of exercise was given; in Experiment III the exercise was increased to 3 times of 20 minutes daily.

Animals were weighed once a week and were killed at the time indicated in table 1. Routine microscopic sections were taken as follows and preserved in 10 per cent formalin: heart—3 complete transverse sections through the base to get as many major branches of the coronary arteries as possible; aorta—sections of ascending arch, descending and abdominal aorta; femoral artery; pulmonary artery; kidney, including renal artery; liver; adrenal; pancreas; spleen; and a few cerebral arteries. Sections were stained routinely with hematoxylin eosin stain. Sections of aorta and coronary arteries were stained by 3 additional methods: Sudan IV following frozen sections for lipids (2), 0.5 per cent toluidin blue for mucopolysaccharide increase in the intima (1, 4), and Verhoeff's elastica stain (2). The degrees of atherosis in the aorta, coronary arteries, and adrenals were indicated as 1 (slight), 2 (moderate), and 3 (advanced). In table 1 these numerals express average degrees of atherosis in more than one animal. In a few lots an animal died before the experiment ended; such animals were excluded.

Experiment I was designed to test the development of atherosclerosis in exercise and non-exercise groups fed two levels of cholesterol dosage. The animals were killed at the end of 6, 8, and 12 weeks. The basal diet controls in Experiment I were not repeated in Experiments II and III.

Experiments II and III were set up to test a possible effect of exercise on the disappearance of cholesterol from the aorta and other vessels after the rabbits had been fed cholesterol for a time sufficient to develop atheromata and afterwards returned to a standard diet during the recovery period, and in Experiment III the exercise was continued.

In Experiment II (table 1) 4 lots of 4 rabbits each were fed two dosage levels of cholesterol for 12 weeks. Two of the lots were exercised during this period and two were not. At the end of this exercise-cholesterol period blood was drawn from the rabbits and chemical

TABLE 2. BODY WEIGHT (GRAMS) AT END OF EXPERIMENT.

| Group No. | % Cholesterol | Exercise (Mins. Daily) | First Period (Weeks) | | | | | | Recovery Period (Weeks) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 6 | | | 12 | | | 4 | | 8 |
| | | | Experiment I | II | III | I | II | III | I | II | III |
| | | | No. of Animals 6 | 4 | 8 | 2 | 4 | 8 | 4 | 8 | 4 |
| 1 | 0 | 0 | 1376 | | | 2207 | 2070 | 1918 | 2433 | 2612 | 2833 |
| 2 | 0 | 20 | 1283 | | | 2215 | 1985 | 1694 | 2320 | 2197 | 2690 |
| 3 | 0.1 | 0 | 1249 | 1181 | 1432 | 2395 | 2058 | 2242 | 2340 | 2670 | 2877 |
| 4 | 0.1 | 20 | 1070 | 1220 | 1235 | 2300 | 2045 | 1889 | 2685 | 2120 | 2413 |
| 5 | 0.5 | 0 | 1084 | 1342 | 1382 | 2175 | 2051 | 2071 | 2286 | 2319 | 2699 |
| 6 | 0.5 | 60 | 905 | 1438 | 1090 | 2185 | 2103 | 1787 | 2513 | 1911 | 2425 |

studies were performed. All lots were then allowed to recover for periods of from 4-10 weeks to see whether the effects of exercise might have been delayed. As mentioned above, in Experiment II no exercise was given in the recovery period. The rabbits were killed and histologic sections were made as described previously.

In Experiment III 4 lots of 8 animals each were fed cholesterol. Two levels of cholesterol dosage were used for 12 weeks, as noted in table 1. Two of the lots (3 and 5) were not exercised but were not sacrificed for from 4-8 weeks after cessation of the cholesterol feeding. The remaining two lots (4 and 6) were exercised during the 12 weeks of cholesterol feeding and during the additional 4-8 weeks following cessation of the cholesterol administration.

## RESULTS

*Chemical and growth studies.*—The growth results of the rabbits are shown in table 2. The exercise decreased the growth and feed utilization of animals receiving different diets.

The serum calcium, phosphorus, and cholesterol determinations are shown in table 3. The calcium and phosphorus contents of the serum were similar in the animals receiving the basal ration with or without cholesterol. Exercise likewise did not show any change in the calcium and phosphorus levels. As the experiments continued, however, both decreased, apparently independently of the tendency for calcium to be deposited in older atherosclerotic lesions.

The serum total cholesterol was increased as

TABLE 3. BLOOD STUDIES OF EXPERIMENT II (MG./100 ML. SERUM).

| Lot No. | Ration | Calcium | | Phosphorus | | Total Cholesterol | | |
|---|---|---|---|---|---|---|---|---|
| | | Age (Weeks) | | Age (Weeks) | | Age (Weeks) | | |
| | | 4th | 8th | 8th | 13th | 4th | 8th | 13th |
| I | Basal, no exercise | 10.8 | 8.1 | 8.2 | 5.5 | 94 | 125 | 36 |
| II | Basal + exercise | 12.1 | 7.4 | 7.9 | 7.5 | 119 | 43 | 42 |
| III | 0.1% Cholesterol, no exercise | 10.9 | 8.3 | 8.8 | 6.1 | 150 | 325 | 350 |
| IV | 0.1% Cholesterol + exercise | 11.8 | 10.1 | 9.6 | 5.6 | 165 | 145 | 192 |
| V | 0.5% Cholesterol, no exercise | 12.9 | 9.0 | 8.4 | 6.2 | 738 | 465 | 1134 |
| VI | 0.5% Cholesterol + exercise | 12.8 | 8.6 | 8.1 | 4.9 | 1242 | 380 | 584 |

levels of cholesterol were increased in the diet. Serum total cholesterol averages were lower in the exercise groups receiving 0.1 per cent cholesterol and 0.5 per cent cholesterol toward the end of the exercise period (Lots 4 and 6) than in the non-exercise groups (Lots 3 and 5). The percentage of free esterified cholesterol remained constant (table 4). The high serum cholesterol in the rabbits fed 0.5 per cent cholesterol was persistent at a high level even 16 weeks after the animals were taken off the test diet; while the serum cholesterol level of the animals fed 0.1 per cent cholesterol returned to normal 5 weeks after the animals were taken off cholesterol.

TABLE 4. PERCENTAGE OF FREE AND COMBINED CHOLESTEROL OF SERUM FROM RABBITS OF LOTS V AND VI AT 13TH WEEK OF EXPERIMENT II.

| Ration | Rabbit No. | Free % | Ester % |
|---|---|---|---|
| Lot V | | | |
| 0.5% cholesterol, | 1 | 13.7 | 86.3 |
| no exercise | 2 | 13.5 | 86.5 |
| | 3 | 13.7 | 86.3 |
| | 4 | 15.1 | 84.9 |
| | Average | 14.0 | 86.0 |
| Lot VI | | | |
| 0.5% cholesterol | 1 | 13.4 | 86.6 |
| + exercise | 2 | 13.4 | 86.8 |
| | 3 | 18.2 | 81.8 |
| | 4 | 20.3 | 79.7 |
| | Average | 16.0 | 84.0 |

*Microscopic examination.*—The organ showing the earliest lipid infiltration was the adrenal (table 1). This was characterized by the replacement of the almost uniformly pink cytoplasm of the normal cortical cells of the zona fasciculata and zona reticularis by pale pink minute granules and vacuoles and a swelling of the cell cytoplasm. These pale swollen cells stained positively with Sudan IV. A good correlation existed between the degree of swelling of the cortical cells and the amount and duration of the cholesterol feeding. The animals receiving the 0.1 per cent diet for 6 weeks showed only moderate swelling and pallor in the middle zone while those receiving 0.5 per cent cholesterol for 12 weeks showed great swelling of the cells with rupture of many foamy cells in all cortical zones. At times the lipoid infiltration was accompanied by focal collections of eosinophils and lymphocytes.

The arch of the aorta and main pulmonary artery were next in order to show early minimal involvement on low dosage over a short period of time. The aortic arch and pulmonary artery were grouped together in table 1, because there was only a slight difference in their degree of involvement, the aortic arch being slightly more advanced. A minor point of difference did exist, however, in the manner of infiltration. In the aorta early involvement usually took three forms, 1) foam cell macrophages appeared beneath the endothelium; 2) fibrillar pale lipid plaques were laid down in the intima, and 3) focal points of pallor, apparently lipid infiltration, appeared in the superficial muscle fibers. In the pulmonary artery, foam cell infiltration was much more prevalent than the fibrolipoid intimal pads so common in the aorta.

A good correlation was found between the degree of aortic involvement and the dosage and duration of the cholesterol feeding. Thus in Lot 3 (table 1, Experiment I), animals receiving 0.1 per cent for 6 weeks showed no infiltration, and the aorta and pulmonary artery of one of the 8 week animals contained a few intimal foam cells. Both 12 week animals on the 0.1 per cent diet contained superficial foam cells and fibrolipoid pads in their aortas. All rabbits ingesting the 0.5 per cent diet showed aortic involvement of both the foam cell and fibrillar lipoid plaque type. In the 12 week animals there appeared beneath the intima strands of spindle cells resembling disorganized muscle cells which covered lipoid plaques at many points and were thought to be regenerating muscle fibers. These became more prominent in Experiment III where the age of the lesions was the greatest.

Calcific deposits were noted in a few of the aortas of the 12 week group on the 0.1 per cent diet and in many of the 12 week 0.5 per cent diet group. In two 0.1 per cent rabbits, calcification of the aortic elastica fibers around the superficial muscle bundles occurred. In two of the 0.5 per cent rabbits numerous foci of calcium appeared deep in the atheromatous plaques at the junction of the media. Here the calcification did not appear to involve the elastica primarily but seemed to have been deposited at random well below the intimal surface. All of the animals showing calcification were 12 week animals so that the calcification apparently depended

mostly on duration of the lesions and to a lesser extent upon degree of involvement. Many rabbits in Experiment III receiving 0.5 per cent cholesterol for 12 weeks showed calcific deposits in the aortic atheromata.

No difference between the types of lipoid deposition in the aortas and coronary arteries of exercised and non-exercised rabbits existed. Each group showed foam cell deposition, fibrillar pad intimal change, and superficial muscle cell lipid infiltration. Similarly no difference was apparent in the type of coronary artery atheroma, nor in those lesions occurring in other arteries or viscera.

The appearance of the aorta and coronary arteries in Experiments II and III showed a few variations from those in Experiment I. Many more atheromata contained foci of calcium. On comparable dosage levels the atheromata seemed to be about the same size, indicating little apparent resorption within the time period indicated in Experiments II and III. Quite often bands of spindle shaped cells resembling muscle reappeared near the lumen, thereby producing a walling-off effect over the subjacent lipoid masses deep in the intima. Likewise, little resorption seemed to have taken place in the adrenals of rabbits in Experiments II and III.

In addition to lesions noted above, lipid macrophages were seen in the interstitial tissue of the heart, lungs, spleen, and kidneys in animals receiving 0.5 per cent cholesterol for 12 weeks.

Sections stained with Verhoeff's elastica stain showed disruption of the superficial elastica fibers by the lipoid material in the plaques. A variable amount of metachromatic material suggesting mucopolysaccharide was seen in the atheromatous plaques and pads with the toluidin blue stain. In some sections this material actually seemed increased over that seen between the muscle fibers of the media.

## DISCUSSION

The maximum degree of arterial atherosis in all rabbits was found in the aorta consistently. With rare exceptions the ascending aorta and arch had the most severe involvement with the number and degree of intimal infiltrations diminishing from above downward. The main branches of the pulmonary artery also showed frequent and extensive involvement. The muscular arteries were next with the coronary and renal arteries showing lesions fairly frequently with the higher cholesterol dosage and much less so with the lower (table 1, Experiment I, Lots 3 and 4 as compared to Lots 5 and 6). Adrenal involvement has been mentioned previously.

Experiment I showed the development of atheromatous deposits in the aorta and major arteries in the exercise and non-exercise groups receiving two levels of cholesterol dosage. The duration and amount of the cholesterol dosage and not the exercise determined the degree of involvement. Those rabbits receiving 0.5 per cent daily (table I, Experiment I, Lot 6 vs. 5) for 6 to 12 weeks had advanced atherosis regardless of exercise, while Lots 4 vs. 3 showed moderate to low involvement depending on dosage and duration. We would assume therefore that the exercise factor as set up in these experiments had no consistent effect on the development of atherosis in rabbits receiving high and low cholesterol dosage. It should be noted that later in the experiment both exercise groups showed lower averages of serum total cholesterol than their cholesterol control groups (table 3). These levels, however, were apparently elevated sufficiently to allow the advanced lesions to develop.

Experiments II and III were set up to test a possible effect of exercise on the disappearance of cholesterol from the aorta and other vessels after the rabbits were fed cholesterol for a time sufficient to develop atheromata then returned to a standard diet during the recovery period. In Experiment II no exercise was given during the recovery period, and in Experiment III exercise was continued. At the end of these experiments, no essential differences were observed in the vessels of animals of any of the three regimes on comparable dosages. This suggests that cholesterol leaves the vessels very slowly, at least up to 5 months. Exercise seemed to have no effect on the rapidity with which cholesterol was deposited in the vessels or adrenals, nor on resorption of cholesterol from the vessels or adrenals.

The longer the experiments ran the greater was the tendency for calcium to be deposited in the atheromata.

SUMMARY

Under the conditions of our comparatively short experiments, exercise had no effect on the development of atheromata in the aorta, coronary arteries, or adrenals of rabbits placed on a high and low cholesterol dietary regime. Similarly exercise appeared ineffective in speeding up the disappearance of cholesterol from the vessels once the atheromata were developed.

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# AGING: A THEORY BASED ON FREE RADICAL AND RADIATION CHEMISTRY

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The phenomenon of growth, decline and death—aging—has been the source of considerable speculation (1, 8, 10). This cycle seems to be a more or less direct function of the metabolic rate and this in turn depends on the species (animal or plant) on which are superimposed the factors of heredity and the effects of the stresses and strains of life—which alter the metabolic activity.

The universality of this phenomenon suggests that the reactions which cause it are basically the same in all living things. Viewing this process in the light of present day free radical and radiation chemistry and of radiobiology, it seems possible that one factor in aging may be related to deleterious side attacks of free radicals (which are normally produced in the course of cellular metabolism) on cell constituents.*

Irradiation of living things induces mutation, cancer, and aging (9). Inasmuch as these also arise spontaneously in nature, it is natural to inquire if the processes might not be similar. It is believed that one mechanism of irradiation effect is through liberation of OH and $HO_2$ radicals (12). There is evidence, although indirect, that these two highly active free radicals are produced normally in living systems. In the first place, free radicals are present in living cells; this was recently demonstrated in vivo by a paramagnetic resonance absorption method (3). Further, it was shown that the concentration of free radicals increased with increasing metabolic activity in conformity with the postulates set forth some years ago that free radicals were involved in biologic oxidation-reduction reactions (11, 13). Are some of these free radicals OH and/or $HO_2$, or radicals of a similar high order of reactivity, and where might they arise in the cell?

The most likely source of OH and $HO_2$ radicals, at least in the animal cell, would be the interaction of the respiratory enzymes involved in the direct utilization of molecular oxygen, particularly those containing iron, and by the action of catalase on hydrogen peroxide. This follows from the fact that it has been known for many years that iron salts catalyze the air oxidation of organic compounds (5, 6, 14, 15); OH radicals are believed to be involved in these reactions (13). Iron salts also catalyze the decomposition of hydrogen peroxide to water and oxygen—a reaction that involves OH and $HO_2$ radicals (16). Further, recent studies in this laboratory on the inactivation of rat liver catalase suggest that the OH radical is involved. The catalase activity of the homogenates both in the presence and absence of hydrogen donors such as sodium bisulfite, sodium hypophosphite, pyrogallol, and mercaptans remains relatively constant under an atmosphere of nitrogen. However, in the presence of air, catalase activity rapidly decreases and the rate of decrease is accelerated in the presence of the hydrogen donors. In addition, methanol, ethanol, and sodium formate (compounds (2) which are oxidized by hydrogen peroxide in the presence of catalase) stabilize the enzyme in the presence of air. A free radical mechanism involving the OH radical has been implicated in the analogous degradation of hemoglobin and myoglobin (7).

Thus, although the evidence is indirect, there are good reasons for assuming that the changes produced by irradiation and those which arise spontaneously in the living cell have a common source—the OH and $HO_2$ radicals. These arise on the one hand through the dissociation of water and on the other largely by the interaction of the oxidative enzymes with oxygen and hydrogen peroxide. (It is not unlikely that other metal-containing enzymes, such as vitamin $B_{12}$, which contains cobalt, also contribute.)

The manner in which a highly reactive radical such as OH would exert its effect on a cell is obscure. However, it would be expected to react for the most part near the area where it

Submitted for publication March 23, 1956.
* This research was performed under the auspices of the Atomic Energy Commission.
Published on a grant from the Forest Park Foundation to the Journal of Gerontology.

was produced and to react with the more easily oxidized substances such as $DPNH_2$ or the reduced form of the flavoproteins. They would also be expected to react to a certain extent with other cellular constituents including the nucleoproteins and nucleic acids. The organic radicals formed in this manner (by removal of a hydrogen atom) could then undergo further reactions, e.g., addition of oxygen leading to the formation of peroxides and other oxygenated compounds, degradation into smaller units, dimerization, etc., such as has been observed in simpler free radical and polymer systems (4). In this manner the functional efficiency and reproductive ability of the cell could eventually be impaired. In addition, since genes would be expected to be attacked occasionally it would be anticipated that mutations and cancer would result every now and then.

In a multicellular organism such as man the effects of cells on each other are superimposed on the above. Some cells are more important than others in maintaining life. For example, as degenerative changes occur in the cells of the circulatory system, the flow of oxygen and metabolites to other cells is interferred with, thus leading to further degenerative changes in them.

In addition to the reactions within the cells themselves, one would expect that there would be also a slow oxidation of the connective tissue by molecular oxygen catalyzed by metals such as iron, cobalt, and manganese.

This theory is suggestive of chemical means of prolonging effective life. For example, maintenance of an increased cellular concentration of an easily reduced compound such as cysteine, which affords some radiation protection, would be expected to slow down the aging process and thereby put off the appearance of the diseases associated with it. As a side effect radiation resistance would be enhanced. Further studies of the effect of hydroxy and other radicals, in the presence and absence of oxygen and easily oxidized substances, on cellular constituents such as DNA and RNA may be quite productive. Some of the implications of this theory both as it pertains to aging and to cancer are now under study. Groups of mice of the AKR and C3H strains, which spontaneously develop lymphatic leukemia and mammary cancer, respectively, are daily being given various radiation protection compounds in their diet. These animals will be followed to determine if the average age at which they develop leukemia or cancer is greater than in the controls. Mice in each group are also being sacrificed at periodic intervals for histologic study.

Consideration of the biochemistry of cancer cells and of the systematic effects in cancer from the standpoint of the theory presented in this paper led to the conclusion that hydrogen donors, such as cysteine for example, might be of benefit in the fields of cancer chemotherapy and nutrition. Preliminary work with ascites tumor and LCS cancer in mice supports this conclusion.

## SUMMARY

Aging and the degenerative diseases associated with it are attributed basically to the deleterious side attacks of free radicals on cell constituents and on the connective tissues. The free radicals probably arise largely through reactions involving molecular oxygen catalyzed in the cell by the oxidative enzymes and in the connective tissues by traces of metals such as iron, cobalt, and manganese.

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# GERIATRIC PRACTICE

## GERIATRIC OFFICE GYNECOLOGY

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The problems of the patient of postmenopausal age are often overshadowed by other more prominent aspects of the aging process. Many symptoms of gynecologic origin are frequently not treated or are minimized because the patient is reluctant to discuss them with her physician. Sometimes elderly women will admit that they have had certain symptoms for some time but they believed that such symptoms are to be expected during that period of their lives. These patients should be encouraged to tell physicians about their symptoms, since they do not have to learn to live with such discomfort when relief can be given to them. The more common of these complaints and their management will be considered in the ensuing paragraphs.

### VULVAR PRURITUS

Vulvar pruritus, a common symptom in women of all ages, receives more attention during the years of sexual activity than at any other time. It varies considerably in intensity and in the annoyance that it causes the patient. Its causes are also varied.

The obese woman with large folds of flesh rolling over the abdomen, huge pendulous breasts, and large thighs, almost always has pruritus of the groin and perianal region. She often will admit having pruritus beneath the breasts as well. However, the discomfort has gradually increased with her gain in weight and is usually accepted as a natural accompaniment to the obesity. The pruritus becomes worse in the summer and during damp weather when perspiration is greatest. The areas that itch have a reddened base, often with brownish pigmentation and mildly edematous skin. In some instances a violaceous tint can be seen. Excoriation may be present; ulcerations are rare. The involved area may include the entire vulva. Scrapings of the affected part on wet spreads may show either fungous spores or hyphae. Cultures (requiring special media) may be made to establish a definitive diagnosis. A working diagnosis of epidermophytosis of the groin or vulva can be made from the physical appearance, and treatment can be initiated without a positive culture. Relief can be obtained by keeping the vulva, groin, and perianal regions as dry as possible. Tight girdles increase the perspiration in this region and prevent ventilation but it is difficult to persuade the patient to discontinue permanently the use of this garment. Dusting powder, especially borated ones, tend to dry the area and inhibit fungous growth. Unsaturated fatty acid powders, such as Desenex ®, will cure the superficial infection. Ointments containing the same drug are especially useful in the perianal region.

A variant of monilial vulvitis with accompanying pruritus is diabetic vulvitis. In the latter condition, the vulva is acutely inflamed with reddened, edematous labia, both majora and minora. This area of discomfort might be the only indication of the onset of diabetes. For this reason, whenever monilial vaginitis is suspected or proved, blood sugar studies and repeated urinalyses are necessary to exclude diabetes mellitus. Even though the blood sugar of patients with monilial vulvitis remains within normal limits, it is our policy to advise restriction of sugars and carbohydrates in the diet as part of the treatment. Such restriction also helps in reducing the patient's weight.

In women with chronic intractable pruritus of the vulva, leukoplakia should be suspected even before examination. These patients have such severe exacerbations of the pruritus at night that insomnia is often the presenting complaint, and symptoms of vulvar pruritus

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Published on a grant from the Forest Park Foundation to the Journal of Gerontology.

may be elicited only with difficulty. The combination of pruritus vulvae and sleepless nights increases the nervous tension of the patient, which, in turn, makes the other symptoms worse. Sedation alone is often only partly helpful, and at times patients may take relatively large amounts of the various barbiturates without relief. Leukoplakic changes of the vulva are not always symptomatic. The cause of the condition is unknown, but it is believed to be due to irritation. Whatever the cause, the only effective treatment has been vulvectomy. Patients with milder lesions and minimal pruritus may be treated with sedation but they should be periodically observed, since malignant change may occur. Because leukoplakia is often the precursor of carcinoma of the vulva, a specimen of any ulcerated area must be obtained for biopsy. Local medication, large doses of vitamin A and cortisone have all been ineffective. Whereas leukoplakia of the vulva may recur after vulvectomy, the risk is not great and the relief afforded is well worth this risk.

Neurodermatitis of the vulva has not been encountered too frequently among women of postmenopausal age, but it can occur. The pruritus produced by neurodermatitis is as intractable as that caused by leukoplakia, and it, too, tends to be exaggerated at night, interfering with sleep. Whereas the labia minora, clitoris, and fourchette are usually involved in leukoplakia, in neurodermatitis these areas are less frequently affected. The skin and mucous membranes become edematous and thickened, with a violaceous hue, in patchy distribution, and with small ulcerated areas from scratching. The patchy distribution is rarely bilateral. Unilateral edema of the vulva may be present. Whatever the cause of the neurodermatitis may be, scratching prevents the lesion from healing. Control of the condition requires absolute refusal to scratch the area. This is difficult to accomplish at night, but with sedation, reassurance, and a modicum of local treatment cure can be effected. A local analgesic ointment is desirable but is not curative. Hydrocortisone and antihistaminic preparations are useful. Podophyllin preparations may be used with caution. In one instance, podophyllin solution caused such acute vulvitis that the patient had to refrain from scratching in order for the lesion to heal. Treatment as vigorous as this, however, is not recommended. In our experience roentgentherapy to the vulva not only is ineffective but is definitely contraindicated.

Vulvar pruritus is sometimes produced by nylon underclothes. Some women complain that nylon garments, such as panties, girdles, and even stockings, cause burning or stinging. We ask all women who have vulvar pruritus if they wear nylon underclothing. Those who do, and have vulvar itching, are often the moderately obese women as well. Tight fitting garments are more commonly involved than loose ones. The vulva, chiefly the non-hair growing areas of the perineum, labia minora, and fourchette, show redness, intracutaneous edema, and often small ulcerated parts. Smear and culture for yeast yield negative results. Relief can be obtained by changing to cotton or rayon garments and use of local cleansing measures.

## VAGINAL DISCHARGE

Increased vaginal secretion may be present in women of any age. The degree of irritation or annoyance that patients have varies considerably. During the years of regular menstruation, the amount of physiologic secretion varies from individual to individual, and often an excessive amount is unreported. Following the menopause, the physiologic secretion of the genital glands is reduced to a minimum, and a return of noticeable vaginal secretions is abnormal. Many women do not recognize the increase in secretion except when it causes chafing, burning, or itching. Some accept this as part of their fate as women.

The cause of a return of vaginal moisture and secretion is vaginitis or cancer. The senile vagina, when it no longer receives the effect of estrogenic hormones, becomes thinner and thinner, so that ultimately it resembles histologically that of an infant. The thinning of the mucous membrane renders it more susceptible to surface infection. The commonest surface infections are those resulting from Trichomonas vaginalis and nonspecific vaginitis. The appearance of the vagina in either instance is similar.

In the normal senile vagina, the mucous membrane is dull without the whitish overlay of the adult vagina. It has lost its rugae and it is considerably less elastic. At times the senile vagina seems transparent, but the whole is homogenous. If vaginitis is superimposed, small bright red spots occurring in groups looking like a "strawberry eruption" can be seen. The

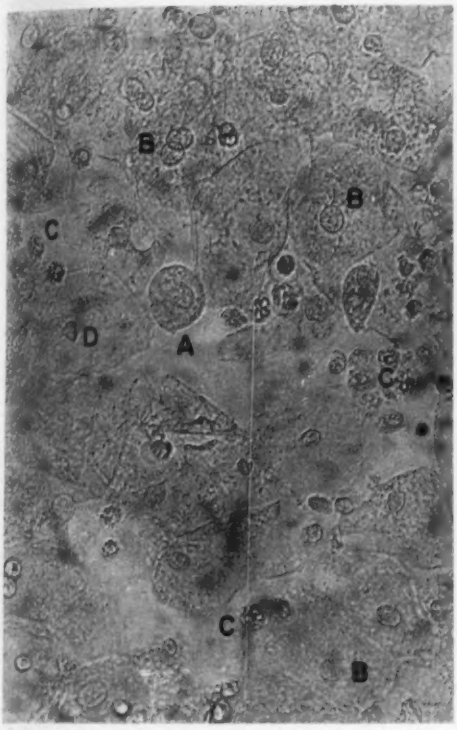


Fig. 1. Fresh vaginal smear (X 130) showing a basal epithelial cell with a relatively large nucleus (A); large numbers of incompletely cornified epithelial cells with vesicular nuclei (B); numerous pus cells (C); and a rare cornified epithelial cell with a compact pyknotic nucleus (D). This is the usual smear in non-specific atrophic vaginitis.

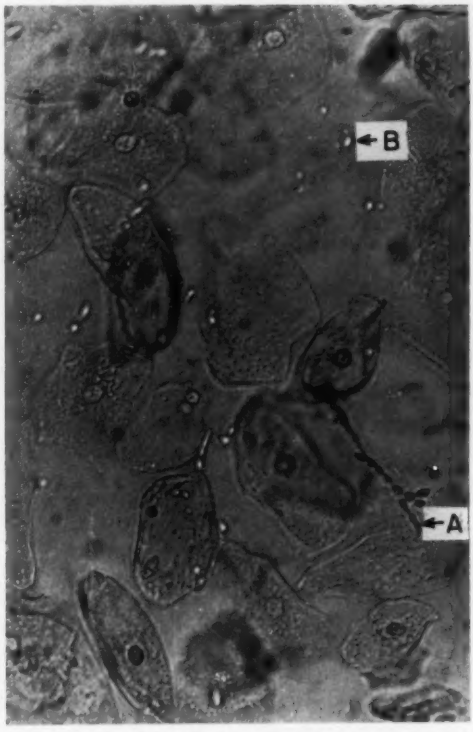


Fig. 2. Fresh adult vaginal smear shows well cornified epithelial cells, numerous yeast hyphae (A), and yeast buds (B). (X 260).

vaginal vault and vaginal portion of the cervix are the chief areas of involvement. The fourchette and hymenal area are usually uninvolved. The differential diagnosis lies in demonstration of presence or absence of Trichomonas vaginalis or Monilia. A wet smear is made by placing a droplet of secretion in a drop of normal saline under a cover slip. Hanging drop preparations are too thick for satisfactory interpretation. Prompt microscopic examination under low and high power magnifications will reveal the relative proportions of 1) pus cells, 2) cornified vaginal epithelial cells, 3) basal vaginal cells, 4) hyphae or budding yeast cells, and 5) trichomonads. Little experience is needed to distinguish between these. In the normal adult vagina, a fresh smear reveals numerous pus cells, many cornified epithelial cells, and few precornified or basal cells with large vesicular nuclei. As the mucosa becomes more atrophic, the tendency toward cornification is reversed, with few cornified cells, many basal cells, pus cells, and red cells (fig. 1). The presence of pus cells is normal and does not indicate infection except if there is an excessive number. Trichomonads are readily identified by the beating of a flagellum that moves the organism around. If the smear is not examined within 10 minutes, these organisms become inactive and are difficult to distinguish from pus cells. Identification by culture is possible, but such cultures are not readily available. Whereas there remains quite a controversy as to whether the Trichomonas vaginalis is a pathogen, nevertheless, when it is demonstrable in an individual with symptoms, relief can be obtained only by its eradication. In our experience it has been a frequent cause of pelvic discomfort in older women. Failure to recover the Trichomonas is sometimes the fault of the patient, who douches before the examination because

"she wants to be clean" when examined. Such patients often require a second examination with douching interdicted.

Vaginitis secondary to Monilia is much less common in women of postmenopausal age than in their younger sisters. The fungus thrives in a moist, sweet medium, when glycogen is increased, as in pregnancy or diabetes mellitus. The fungus does not grow well in the atrophic vagina. When it does, it is characterized by yellow white material which resembles curds. The exudate is loosely attached to the mucosa and when wiped away leaves a bright red ulceration. A fresh smear of the vaginal secretion will show a tangled net of hyphae, pus cells, and yeast buds (fig. 2). Cultures, which are readily available, will support the diagnosis.

The diagnosis of vaginitis of nonspecific origin is made by exclusion of trichomonas, yeast, and possibly in rare instances, Neisseria. Such a lesion has a thin, purulent discharge containing many pus cells, uncornified epithelial cells, and a wide variety of bacteria. No specific bacterium is at fault, and cultures show E. coli, Streptococci, Streptobacilli, and Micrococci in abundance.

Treatment of infections of the vagina depends upon the cause. A wide variety of modes of treatment of Trichomonas vaginitis are in vogue. These include home treatment by douching, local application of arsenical preparations, use of iodoquinolin drugs, and an oral preparation, Tritheon ®. Treatment should be initiated in the office with scrubbing of the vagina with green soap, or a detergent solution, and insufflation with a preparation such as Floraquin powder ® or Tricofuron ®. The patient should continue treatment at home with use of mildly acid douches followed by suppositories of the same medication for 7 to 10 days. Because Trichomonas infestation is difficult to eradicate, the cycle should be repeated 30 days later. We have had no experience with treatment by oral medication.

Fungous infections of the vagina respond satisfactorily to the unsaturated fatty acid preparations, such as Propion-gel ®, and to Mycostatin ® vaginal tablets. The latter, an antibiotic preparation, is not only effective but also has the advantage of being esthetically attractive to the more fastidious patients. Restriction of sugar and carbohydrates in the diet is also urged upon these patients, and diabetes must be excluded.

Nonspecific vaginitis is best controlled by restoring the mucosa to a resistant one by local use of estrogenic hormones. The senile vagina responds well to hormone creams, or suppositories, with cornification of the superficial layers and a change in the pH from alkaline to acid. Symptomatic relief following use of such hormone creams will be accompanied by a change in the type of cell desquamated in the fresh smear, so that clinical cure will be complete when the majority of cells in the fresh smear show evidence of cornification. Such cases usually require application of a cream for one week but may require a maintenance dose again after 6 to 8 weeks. It is usually unwise to administer hormones orally or intramuscularly for atrophic vaginitis because of the undesirable side effects upon the breasts or the endometrium.

Patients having recurrence of any type of vaginitis sometimes require a combined form of treatment. It may be desirable, for example, to treat Trichomonas vaginitis in women of postmenopausal age with both trichomonacidal agents as well as local hormone creams. It has been our experience that antibiotic vaginal suppositories, other than Mycostatin, have little additional value.

## VAGINAL BLEEDING

The distressing recurrence of vaginal bleeding or a bloody discharge long after the menopause is a danger signal, well recognized both by the physician and patient. Every educated woman now recognizes this as a sign of cancer, and the patient immediately asks, "Do I have cancer?" Too often she does. Certainly, it must be considered in the differential diagnosis. Examination to exclude malignant lesions must include careful inspection and palpation of the genitals and appropriate laboratory tests. Inspection may reveal an irritated urethral orifice that has bled from trauma with toilet tissue. A small percentage of patients have chronic urethritis or a urethral caruncle that causes a bloody discharge. In others, senile vaginitis is the cause. Cervical polyps, although infrequently, may cause bleeding, especially postcoitally. Carcinoma of the vagina, cervix, or fundus must be eliminated as possible causes of vaginal bleeding. If inspection fails positively to identify the cause of bleeding, additional study is necessary. A Papanicolaou spread from the cervix or vaginal secretions is desirable and available to most physicians. In this manner, malignant cells can

be identified, although search must be made for their source. Bloody discharge of undetermined origin is an indication for diagnostic curettage or biopsy with use of an anesthetic. It is better to err by overexamination of the patient than to allow a malignant tumor to escape detection. Difficulty in visualizing the cervix or vaginal vault is often encountered in older women in whom cicatricial contracture of the vaginal vault has occurred. In these, examination with use of an anesthetic is mandatory.

## PELVIC PAIN

Pelvic pain is described by the elderly woman in many ways. To her it may be simply vague pressure on the bladder, rectum, or vagina. She may express it as a "bulging sensation," "inability of her bowels to move," or "a feeling of incomplete emptying of the bladder." Pain in the pelvis in women of postmenopausal age rarely is acute, as in torsion of the pedicle of a viscus, i.e., ovarian cyst, and much more often has progressed slowly. The principal cause of pelvic discomfort in women of postmenopausal age is relaxation of the pelvic supporting structures resulting in cystocele, procidentia, or enterocele. These conditions may cause only mild symptoms, but the amount of relief obtained following their correction is often surprising.

The discomfort related to cystocele is referred to the suprapubic region and to one or both inguinal areas. It is exaggerated by standing, straining, and sometimes by wearing a corset. The association of urinary incontinence, frequency, or incomplete emptying of the bladder may not be noted by the patient, but she may remark on questioning that she has to "push the bladder up" to void. A sense of fullness in the vagina is often present.

When uterine prolapse occurs, symptoms may be minimal until the entire vagina is everted. Patients deny that complete procidentia causes discomfort but admit that the presence of the "lump between their legs" is annoying. However, many are incapacitated because the prolapsed viscera interfere with their activity. Some seek medical aid only because the prolapsed cervix becomes ulcerated as a result of trauma. Surprisingly, bladder dysfunction may be minimal.

The discomfort of enterocele (fig. 3) is commonly referred to the back or rectum. This pain is also vaguely described by the patient. She

Fig. 3. A large enterocele with atrophic ulcer of the vaginal mucosa.

may notice that it is exaggerated when she attempts to defecate. Some describe a sense of fullness in the vagina. A large rectocele may be difficult to differentiate from enterocele, but in either instance, surgical repair is necessary.

Clinical differentiation of these types of hernias sometimes requires expert consultation. However, considerable relief can be given by fitting the patient with a proper sized pessary. Pessaries of the Smith and Hodge types are not as effective in women of postmenopausal age as in their younger sisters. For temporary relief, a doughnut pessary (fig. 4) or a Gelhorn pessary (fig. 5) gives the most relief. If procidentia is found, coitus is generally not important; hence obliterating the vaginal function with such an agent causes no concern. The pessary should be large enough to be supported by the levator muscles, and not to be extruded with moderate straining. If too tight, it will be uncomfortable and cause ulceration. In poor

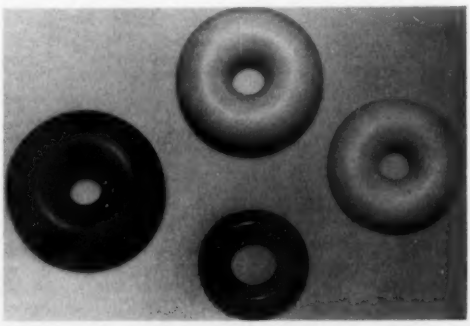

Fig. 4. Doughnut pessaries of various sizes are made of hard rubber, foam rubber, or hollow rubber. Hard rubber pessaries tend to cause ulceration, and hollow rubber ones are easiest to insert.

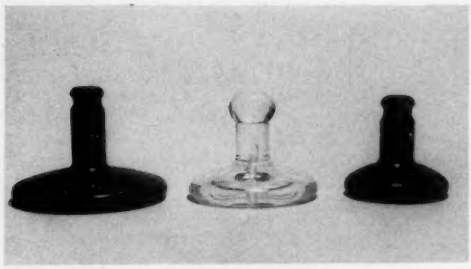

Fig. 5. Gelhorn pessaries are hard rubber or plastic. The handles aid in their insertion and they may be held in place with T-binders or sanitary pads.

risk patients, a properly fitted doughnut pessary can be worn indefinitely, provided it is removed, cleansed, and replaced at intervals of 4 to 6 weeks. Douches are of little benefit, but sitz baths help maintain cleanliness.

Definitive treatment of these conditions is, of course, surgical. Modern methods of anesthesia, preoperative, and postoperative care have reduced the risk, so that seldom is a poor risk patient encountered who cannot be cured surgically. In most instances, the relief obtained is well worth the effort to obtain surgical correction.

Finally, a word about hormones. The average woman who has passed through the menopause soon adjusts to diminished ovarian function. The transition between the bloom of the fertile years and complete senescence is gradual, requiring years to become complete. Changes are both physical and mental, with periods of frustration, anxiety, and emotional instability. When these symptoms occur near the menopause, estrogen deprivation is often assumed to be the cause, even though menses may be regular and normal. Hot flashes are immediately attributed to the menopause by many physicians, even though they may occur for a decade before or after the last menstrual period. "Menopausal syndrome" often is a wastebasket diagnosis, to cover up a physician's haste in disposing of vague emotional or mental distress. Many such patients will give a history of a "series of shots," with relief after a time, only to have recurrence of their discomfort, anxiety, and nervousness later. More satisfactory relief can usually be obtained by allowing the patient to describe her problems and by prescribing mild sedation. Reassurance, interest, and sympathetic understanding are of more therapeutic value than a bucketfull of "shots." Only about 5 per cent of women undergoing the menopause need hormones, administered cyclically and orally. The remainder need little more than temporary respite from their environmental problems.

The patient who is well beyond the menopause needs sex hormones only under two circumstances. The first, previously mentioned, is for local application in atrophic vaginitis. The second indication for sex hormones is osteoporosis, which may be troublesome to geriatric patients. Combined estrogen-testosterone oral preparations are satisfactory for this purpose. Cyclic administration of these hormones should be accompanied by periodic examination of the pelvic organs and breasts.

# BOOK REVIEWS

MENTAL DISORDERS IN LATER LIFE, second edition, edited by Oscar J. Kaplan. Stanford University Press, Stanford, California, 1956, 508 pages, $7.50.

Dr. Kaplan's two volumes on *Mental Disorders in Later Life* have appeared over a 10-year period during which concern and interest in the aged have increased at a rate far in excess of that characterizing the decades before 1945. The first edition (1945) has been widely quoted as a source book summarizing physiologic, sociologic, psychologic, psychiatric, and other medical information about older people. These same areas of information are reviewed, and in several chapters brought up to date by including more recent material, and three new directions of interest are represented—genetics, nutrition and general health status, and the use of electric shock therapy in older patients.

Pollock's chapter (first edition) on statistics of mental disorders in later life is replaced by a similar one prepared by Benjamin Malzberg. The data now bring us up to 1948-1950; and economic status, education, and marital status also are treated in analyzing the first admissions to New York state and licensed hospitals for mental disease for the fiscal year ending March 31, 1948.

McCay's chapter on "Food for the later years" deals more broadly with nutrition in health among older individuals than did Wexberg's earlier brief chapter which concentrated on mental disease and metabolic disturbance, with a plea for better understanding of the socio-economic factors in aging—"One of the more important causes of quantitative undernourishment in old age . . . is probably a socio-economic one." McCay nicely points out the "vast reservoir of human knowledge (in the field of nutrition) extending over many centuries;" relates nutrition, mental disease, and malnutrition; reviews both the nutritional needs and the means for achieving and meeting the goals of adequate nutrition in older people, in mental hospitals and in other situations; and also introduces into the field of nutrition among the aged the concepts and practices of community education and action.

Kallmann's chapter on genetic aspects of mental disorders in later life is illustrated by photographs of 8 sets of twins and draws upon the data from twin studies familiar to the reader who has known of Kallmann's contributions in the study of tuberculosis, schizophrenia and other disorders, aging, and longevity. "It is demonstrated by observations of this kind that fully recorded twin data are helpful in investigating the challenging problems posed by severe maladjustment to aging and old age. Beyond question, further advancement in the understanding of involutional, arteriosclerotic, and senile psychoses will require the planning of more basic research in relation to the interplay of such complex determinative components as age-susceptible personality traits, reduced adaptive (homeostatic) plasticity, and those gene-specific biochemical phenomena controlling growth and decline. It seems rather certain, however, that adequate progress in the management of the clinical and psychological aspects of geriatrics will not be possible without a more thorough knowledge of the genetic background factors, which primarily determine man's variable capacities for maintaining a state of physical and mental health throughout life, including the senium."

The chapter on electric shock therapy by Prout, Allen, and Hamilton is a departure from the pattern of the first edition and from the other chapters of this second volume in that it presents a specific therapeutic method for "disordered emotional states" among patients past 60. The authors review the literature on EST and point to the refinements of technique since its introduction in 1938 and the increased experience with EST. The necessity for understanding the individual's life history and his physical illnesses and resistance to these illnesses prompts the writers to urge consideration of 1) the nature of the mental illness against which EST is to be used, 2) the previous therapies attempted, 3) the adequacy of the cardiovascular system, and 4) curarization to reduce complications of EST.

In addition to these new contributions, the authors who have written for both editions have revised their chapters in varying degrees. This new edition contains 19 chapters, over 500 pages and more than 950 bibliographical references; a gain of about 17 per cent in pages and 30 per cent in number of references to published literature over the 1945 edition of *Mental Disorders in Later Life.*

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BIOLOGY OF SENESCENCE, by Alex Comfort. Rinehart & Company, Inc., New York, 1956, 257 pages, $4.00.

The monograph by Comfort constitutes a most significant critical review of existing facts and theories pertaining to senescence in animals and men. The author in his unbiased and unemotional approach to the subject avoids summary condemnation of theories currently considered obsolete, pointing out that some of the theories have a few facts on their side. He convincingly demonstrates the fallacy of generalizations, and in his examination of analogies based on religious, poetic, metaphysical, and philosophical literatures on senescence, skillfully succeeds in disassociating facts and logical conclusions about senesence from philosophy.

The book contains 6 main chapters: The Nature and Criteria of Senescence, The Distribution of Senescence, Senescence in Protozoa, The Influence of Genetic Constitution on Senescence and Longevity, Growth and Senescence, and The Mechanism of Senescence. In the very important first chapter, dealing with the nature of senescence, the forms of senescence (mechanical senescence; "accumulation" and "depletion"; morphogenetic senescence) and senescence in evolution are discussed in special subsections. The reading of this part of the book, in which the deductions and conclusions by Comfort constitute the greater part of the text, is particularly rewarding to the reader. The very high quality of

presentation is maintained throughout the monograph with the result that a considerable measure of clarity is provided in a field which to a greater extent than most other scientific areas has been dominated by speculation. In spite of the complicated character of the subject the acquisition of the contents of the book is not too difficult; the scholarly presentation and the fact that all the chapters are written by the same author are to a large extent responsible for the comparatively easy reading of the monograph.

The literature list includes 876 references, 25 of which are to publications in Russian journals. It is of some interest to note that less than 1 per cent of the titles refer to publications prior to 1850. Of the remaining publications about 3 per cent date from the period 1850-1899; after 1900 the percentage distribution is approximately as follows: 1900-1909, 3%; 1910-1919, 6%, 1920-1929, 15%, 1930-1939, 28%, 1940-1949, 25%, and 1950-1954, 20%.

The present book in the reviewer's opinion must be classified as the most important review to date on the biology of aging.

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GERIATRI, by Sten Eckerström and Torben Geill. Rosenkilde and Bagger, Copenhagen, 1955, 216 pages, Dan. kr. 26.50.

The textbook consists of 19 chapters written in Swedish (Eckerström) and Danish (Geill). The book is intended as an introduction to geriatrics for medical students and young physicians and in this respect must be considered a valuable contribution to the medical literature. It has not been the authors' intention to give a detailed analysis of the medical aspects of diseases in old persons, but several of the chapters contain so many pertinent facts that the information may also prove of value to physicians with more advanced training. The most outstanding section in the book is, in the reviewer's opinion, the 33-page chapter by Geill on cardiovascular diseases in old subjects. The outline of the symptoms, signs, and therapy of these disorders is of a very high quality and reflects the author's long experience and sound clinical judgment.

Besides the purely clinical sections the textbook also contains brief chapters on the history of geriatrics; the anatomic, psysiologic, and biochemical aspects of aging; the socio-economic problems of old patients; rehabilitation; and occupational therapy. These chapters serve as a background and supplement to the main sections of the book dealing with the clinical problems of old age diseases.

In contrast to several other textbooks in this field the monograph by Eckerström and Geill is strictly limited to the clinical conditions encountered in old persons. This is of advantage to the readers who must be presumed to be acquainted with the manifestations of the diseases in young adults. Since the book is intended chiefly for Scandinavian readers, a high percentage of the 334 literature citations refer to Danish and Swedish publications (38 per cent). References to American literature are, however, even more numerous (40 per cent); most of the remainnig references concern publications in British (10 per cent), German (7 per cent), and French (5 per cent) journals.

The textbook can be greatly recommended to physicians familiar with the Scandinavian languages.

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St. Louis, Mo.

## BOOKS RECEIVED

Books received since April 1 are acknowledged in the following list.

*Biology of Senescence*, by Alex Comfort. Rinehart & Company, Inc., New York, 1956, 257 pages, $4.00 (reviewed in this issue, page 307).

*Clinical Recognition and Management of Disturbances of Body Fluids*, by John H. Bland. W. B. Saunders Company, Philadelphia, 1956, 522 pages, 109 figures, $11.50 (Chapter 9: Metabolic Changes Peculiar to the Aging and Aged: Diagnosis and Treatment).

*Diseases of the Chest*, by H. Corwin Hinshaw and L. Henry Garland. W. B. Saunders Company, Philadelphia, 1956, 727 pages, $15.00.

*Geriatri*, by Sten Eckerström and Torben Geill. Rosenkilde and Bagger, Copenhagen, 1955, 216 pages, Dan. kr. 26.50 (reviewed in this issue, page 308).

*Mental Disorders in Later Life*, second edition, edited by Oscar J. Kaplan. Stanford University Press, Stanford, Calif., 1956, 508 pages, $7.50 (reviewed in this issue, page 307).

JOURNAL OF GERONTOLOGY

VOLUME 11, NUMBER 3
JULY, 1956

# Section B

## Psychological and Social Sciences, Social Work and Administration

VOLUME 11, SECTION B JULY, 1956 NUMBER 3

# PROBLEM SOLVING SET IN DIFFERENT AGE GROUPS*

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In discussions about older people, one frequently encounters such terms as "set in their ways," or "conservative," or "rigid." These ideas are often behind programs for compulsory retirement in industry. A popularly accepted measure of such behavior is available in tests of problems solving set. This may be defined as the tendency to continue the use of a given method, because it has previously been effective, in the solution of later problems in a series.

The present study is concerned with the relationship between increasing chronologic age and: 1) susceptibility to set, 2) ability to overcome set, and 3) the relative effectiveness of attempts to train subjects to avoid set. There are reasons for expecting age differences in these variables. Ruch (6, 7), Strong (9), and Hinshaw (4), from studies of interests, attitudes, and opinions, indicate that older people are more conservative and show a resistance to change. This resistance might also enter into problem solving behavior. Overcoming the influence of problem solving set involves an ability to change one's approach or point of view.

Thorndike's demonstration of a drop in learning ability with advancing age may also be cited. Whereas Thorndike (10) attributes this change primarily to lack of practice and decreased interest, motivation, or opportunity for learning, Wechsler (11) ascribes the drop to progressive organic deterioration. Problem solving set interferes with new learning; if the present study finds older people more set, any evidence that the effects decrease with training would make an explanation in terms of organic deterioration less plausible.

*Tests of problems solving set.*—Luchins' Water Jars Test is perhaps the most commonly used measure of problem solving set and has served as a prototype for many variations. This test consists of a series of problems in which, given three water jars, each holding a different amount, the subject is required to get a prescribed amount of water. Samples of the items used in the test follow:

| Capacity in Quarts of Containers Given | | | To Get | Description |
|---|---|---|---|---|
| *a* | *b* | *c* | | |
| 29 | 3 | — | 20 | Explained example. |
| 21 | 127 | 3 | 100 | Set inducing problems calling for b-a-2c solution. |
| 23 | 49 | 3 | 20 | Criticals, permitting either b-a-2c or a-c solutions. |
| 28 | 76 | 3 | 25 | Extinction problems, not soluble by b-a-2c |

The first problems are soluble by a common method and the subject usually comes to adopt this as the effective approach. If the three jars were labeled a, b, and c, an expression of the "formula" would be b-a-2c. Eventually, problems are introduced in which either this formula or a simpler one, a-c, will work. Next, an "extinction" item is introduced which cannot be solved by the long method. This may be followed by other ambiguous or "critical" items which can be solved either way.

In a monograph (5), Luchins reports giving the test to over 9,000 subjects, mainly grade school students. A number of studies have been conducted by others attempting to relate similar measures to ethnocentrism and to anxiety, with generally conflicting results. Age differences among subjects were often ignored and never systematically investigated.

Two studies are particularly important as logical foundations for the present investigation. Guetzgow (3) offered evidence that ability to surmount set (shown with the extinction items) and susceptibility to set (shown by set solutions of the critical problems) are separate phenomena representing different abilities. The second study is by Schroder and Rotter (8), who demonstrated the effect of reinforcing the use of new alternatives on problem solving set. Their subjects with more diverse training were better able to adjust to a simpler solution procedure in a series of problems when it became possible to do so.

* This investigation was performed in 1955 as a doctoral dissertation in Psychology at the University of Florida, under the direction of Dr. R. H. Waters.

Cowen, Wiener, and Hess (2) have offered data indicating that an alphabet mazes test, which they developed, is significantly correlated with a version of the Water Jars Test. These mazes tend to build up a habit in which the subject takes a characteristic, indirect path from start to finish. Then a shorter path is also made available. On the extinction problem a new path must be used. An example of the type of problem they used follows:

*Start

A X G R V H
L O K Q I V
B V Z S J K
G Q B X W N
P E Z M A O
D N O B R I

Finish*

The subject is instructed to find a continuous path of words from the upper right hand corner to the lower left hand corner. He is allowed to go one letter at a time in any direction. The problem shown is one of the critical type. Note that two solutions are possible. The direct path spells out "His bed." The set path spells "His war bond." On the extinction item, neither of these paths led to a solution. The subject had to find a new path similar to that used in one of the practice items.

This test provides a type of alternative measure for use in assessing training effects on set behavior. By giving the two tests in counterbalanced order and interposing an explanation after the first test given, it should be possible to assess age differences before and after a standard amount of training.

*Hypotheses.*—Three specific null hypotheses to be tested may be expressed as follows: 1) There are no age differences in susceptibility to problem solving set, 2) The ability to overcome or surmount an experimentally induced set is unrelated to age, and 3) The effect of training in avoiding problem solving set is unrelated to age.

## MATERIAL AND METHOD

*Subjects.*—Each of the three age groups was composed of 50 male and 50 female subjects. All were living in Florida at the time they were tested. The older group, composed mainly of retired people, ranged in age from 50 to 85 (median age 66.02). The middle group ranged in age from 20 to 49 (median age 31.75). The younger group ranged in age from 14 to 19 (median age 16.05).

An attempt was made to obtain subjects in each age group who were comparable to each other and representative of the general population in education and occupation. United States Census figures (1952) for these categories were used as bases and subjects were recruited to fit them. The groups obtained were somewhat above average and fairly representative of the "middle class" population as compared to census figures, since those having very low intelligence were not able to comprehend the task.

Subjects in the older group were generally tested individually or in pairs in their own homes or apartments. Those in the middle-age sample were most often tested individually at their working place, during or after working hours. Younger subjects were mostly volunteers from high school study-halls and classes. Nearly all of these were tested in groups of two or three.

*Tests.*—Cowen, Wiener, and Hess (2) had demonstrated the comparability of the water jar and alphabet maze type tests. However, preliminary studies showed that the forms they used with college students were much too difficult for subjects of the type used in the present sample. Accordingly, a simpler form of the water jars test was adopted from Cowen and Thompson (1), and the alphabet mazes test was modified and made simpler (see Appendix page 316). Both tests were put into the form of small booklets with each problem on a separate page. This allowed subjects to work at their own pace.

The format of the two tests was similar and the directions were as nearly the same as the content of the tests permitted. Items 1 and 2 were practice items and were explained. The third was a "control" item to determine whether the subject would work the problems in the direct way or the long way before the set was built up. Items 4 through 8 were set inducers. These were soluble in the long way but not by the direct method. Items 9 through 12 were "critical" in that they could be solved either by the set method or a more direct one. These offered a potential susceptibility score of 0 to 4. Following item 12 was a page with instructions to stop and wait for a signal before going ahead. Beyond this was item 13, the "extinction" item, which could not be solved in the set manner.

The separate answer sheet was mimeographed with biographic data blanks at the top for classifying subjects as to age, sex, education, and occupation.

The standard explanation, read aloud after completion of the first test was:

"Did you have any trouble with the last problem? Many people do. The trouble is they have found a method that worked on the other problems every time. They try to use it on the last one too and it just doesn't work.

(Experimenter explains last problem if necessary.)

"Another thing you may or may not have noticed is that several other problems just before that last one could be solved *two ways*. One of these would ordinarily be considered easier. Chances are pretty good that anyone coming to those later problems right after reading the instructions would work them the simplest of the two ways.

(Experimenter explains "critical" items.)

"However, if you have just worked a series of other problems using the longer method, you are likely to just go on using the long way wherever it leads to an answer.

"This sort of habit can be useful, but it can also lead to trouble and unnecessary work. You may be so used to thinking of only *one way* of getting an answer that you give up rather than try another way on the *last* problem. The old way doesn't fit on it. To solve it you have to change to a new method and when you do the solution is simple.

"The next series of problems will be of a *different kind*. Try to avoid falling into just one set way of solving them. Remember the advantage of being ready to try a new method."

*Procedure.*—All of the testing was done by the author. Usually, he sat with the subjects at a table or desk. Subjects were told that this was not a test of their individual ability but rather a puzzle on which it was expected different age groups might work differently. The directions were read aloud by the experimenter while each subject read them to himself. Questions about the material were answered as simply as possible, usually by repeating part of the directions.

A few subjects gave up on the Water Jars Test because they had no real conception of what plus and minus and equals signs meant, although they claimed to follow the directions. These individuals may have been able to comprehend the use of these symbols when written for them but seemed to have no capacity to use them to solve new problems. Similarly, on the Alphabet Mazes, a few seemed totally unable to understand the idea of a continuous path of words. Naturally, these subjects had to be eliminated.

Where only one person was being tested, he was told immediately upon arriving at the "stop" page to go on to item 13. In the groups, this was usually the case also. Five minutes were allowed for the completion of this item. If one subject reached the stop page just ahead of another, he usually was told to wait until the other finished. Then they could begin together and timing was simplified.

When the first test was finished, the standard explanation was given. Then the second test was administered in the same way as the first. At the end of the second test, the purpose of the experiment was generally explained in simple terms.

If the subject solved all 4 critical items in the set way he received a score of 4. If he solved them all in the direct way, his score was zero. If he worked 2 in the set way and then saw the direct way and changed, his score was 2, and so on.

For the extinction score, a direct solution within 2½ minutes was scored zero. Direct solution within 5 minutes was scored 1 and no solution within 5 minutes was scored 2. Solutions other than the direct one were usually cumbersome and were scored 1 if they were at all acceptable.

## RESULTS

The first question to be considered was whether the two tests could be combined for such comparisons as before and after training. Significant $t$ ratios were obtained between them for both scores, however. The Water Jars Test tended to be more set-inducing and simply combining the scores would be unacceptable.

Another question concerned the combination of the susceptibility and extinction scores for a total "set" score. This would offer a wider dispersion with a subsequently better chance of finding significant differences. However, the two scores represent learning and extinction measures, which are traditionally treated as separate.

Accordingly, 4 separate analyses of variance were set up, 1 for each of the 2 tests and for each of the 2 scores. The summaries are presented in tables 1 through 4. Each table allows $F$ ratio comparisons for 3 age groups, 2 sex groups, 2 order of presentation groups, and the various interactions among these. The within variance is used as the error term in each.

*Analyses of variance.*—From the summaries, a number of relevant relationships emerge:

1) Age group $F$'s are consistently significant, reaching the 0.1 level for 3 measures and falling just short of this for the fourth.

TABLE 1. ANALYSIS OF VARIANCE SUMMARY FOR WATER JARS SUSCEPTIBILITY.

| Source of Variation | Sum of Squares | d.f. | Mean Square | F |
|---|---|---|---|---|
| Between age groups (A) | 23.3267 | 2 | 11.6634 | 5.7788** |
| Between sex groups (B) | 1.4700 | 1 | 1.4700 | |
| Between orders (C) | 41.0700 | 1 | 41.0700 | 20.3488** |
| Interaction A×B | 18.6294 | 2 | 9.3147 | 4.6151* |
| Interaction A×C | 16.3802 | 2 | 8.1901 | 4.0579* |
| Interaction B×C | 1.4700 | 1 | 1.4700 | |
| Interaction A×B×C | 1.2104 | 2 | .6052 | |
| Within | 581.2800 | 288 | 2.0183 | |
| Total | 684.8367 | 299 | | |

* Significant at .05 level; ** Significant at .01 level.

TABLE 3. ANALYSIS OF VARIANCE SUMMARY FOR WATER JARS EXTINCTION ITEM.

| Source of Variation | Sum of Squares | d.f. | Mean Square | F |
|---|---|---|---|---|
| Between age groups (A) | 15.8600 | 2 | 7.9300 | 17.5793** |
| Between sex groups (B) | .1633 | 1 | .1633 | |
| Between orders (C) | 2.0833 | 1 | 2.0833 | 4.6183* |
| Interaction A×B | 1.4067 | 2 | .7083 | 1.5602 |
| Interaction A×C | 3.2533 | 2 | 1.6266 | 3.6059* |
| Interaction B×C | .0834 | 1 | .0834 | |
| Interaction A×B×C | 1.4800 | 2 | .7400 | |
| Within | 129.9200 | 288 | .4511 | |
| Total | 154.2500 | 299 | | |

* Significant at .05 level; ** Significant at .01 level.

2) Sex group *F*'s are not significant for any measure.

3) Order of presentation is significant on only 2 of the 4 scores, susceptibility and extinction for Water Jars Test.

4) None of the interaction *F*'s is significant for the Alphabet Mazes susceptibility or extinction scores.

5) Age-sex and age-order interactions are significant for extinction scores on the Water Jars Test.

*Analysis of mean differences.*—The analyses of variance allow broad conclusions about the existence of general differences but they do not indicate the specific nature of these differences. In order to gain this sort of understanding, additional comparisons must be made. Table 5 lists the *t* ratios for the different age groups. Sex groups are combined for these comparisons. This table enables us to make the following more detailed analyses of the significant relationships revealed by the *F* tests:

1) On the first test, the 3 age groups show generally increased set with increasing age. It is apparent that the older group shows more set than the middle group in all 4 comparisons for the first test. Only 1 of these differences is significant however. The older group is more set than the younger group on 3 of the 4 comparisons and significantly so on the Alphabet Mazes susceptibility. The middle group is more set than the younger group in 3 measures but significantly less set on the Water Jars extinction score.

2) Data for the second test show that the middle-age group benefited most from the training and the older group benefited least. The middle group is significantly superior to the older group on every measure. However, it is also significantly better than the young group on both susceptibility scores. The older subjects show more set than the younger on all 4 measures, and significantly more on the Alphabet Mazes susceptibility and Water Jars extinction scores.

TABLE 2. ANALYSIS OF VARIANCE SUMMARY FOR ALPHABET MAZES SUSCEPTIBILITY.

| Source of Variation | Sum of Squares | d.f. | Mean Square | F |
|---|---|---|---|---|
| Between age groups (A) | 47.1200 | 2 | 23.5600 | 9.5427** |
| Between sex groups (B) | 3.4133 | 1 | 3.4133 | 1.3825 |
| Between orders (C) | .0133 | 1 | .0133 | |
| Interaction A×B | 1.7867 | 2 | .8934 | |
| Interaction A×C | 14.1067 | 2 | 7.0534 | 2.8569 |
| Interaction B×C | 1.9201 | 1 | 1.9201 | |
| Interaction A×B×C | 13.5199 | 2 | 6.7600 | 2.7381 |
| Within | 711.0400 | 288 | 2.4689 | |
| Total | 792.9200 | 299 | | |

** Significant at .01 level.

TABLE 4. ANALYSIS OF VARIANCE SUMMARY FOR ALPHABET MAZES EXTINCTION ITEM.

| Source of Variation | Sum of Squares | d.f. | Mean Square | F |
|---|---|---|---|---|
| Between age groups (A) | 6.8067 | 2 | 3.4034 | 4.6514* |
| Between sex groups (B) | .9633 | 1 | .9633 | 1.3165 |
| Between orders (C) | .9633 | 1 | .9633 | 1.3165 |
| Interaction A×B | .0467 | 2 | .0234 | |
| Interaction A×C | 1.6067 | 2 | .8034 | 1.0980 |
| Interaction B×C | .9634 | 1 | .9634 | 1.3167 |
| Interaction A×B×C | .1266 | 2 | .0633 | |
| Within | 210.7200 | 288 | .7317 | |
| Total | 222.1967 | 299 | | |

* Significant at .05 level.

TABLE 5. COMPARISON OF DIFFERENT AGE GROUPS ON THE FIRST AND SECOND TEST, FOR COMBINED SEX GROUPS.

First

| N=50 for each Group | Susceptibility | | | | Extinction | | | |
|---|---|---|---|---|---|---|---|---|
| | Alphabet Mazes | | Water Jars | | Alphabet Mazes | | Water Jars | |
| | Old | Middle Aged | Old | Middle Aged | Old | Middle Aged | Old | Middle Aged |
| M | 3.32 | 2.84 | 3.54 | 3.44 | .94 | .74 | 1.22 | .76 |
| $s^2$ | 1.90 | 2.91 | 1.60 | 1.31 | .83 | .77 | .46 | .43 |
| $sm^2$ | .0380 | .0582 | .0320 | .0262 | .0166 | .0154 | .0092 | .0086 |
| t | 1.5474 | | .4146 | | 1.1179 | | 3.4483** | |
| | Old | Young | Old | Young | Old | Young | Old | Young |
| M | 3.32 | 2.64 | 3.54 | 3.56 | .94 | .70 | 1.22 | 1.12 |
| $s^2$ | 1.90 | 2.93 | 1.60 | 1.50 | .83 | .75 | .46 | .35 |
| $sm^2$ | .0380 | .0586 | .0320 | .0300 | .0166 | .0150 | .0092 | .0070 |
| t | 2.1879* | | .0803 | | 1.3498 | | .7855 | |
| | Middle Aged | Young | Middle Aged | Young | Middle Aged | Young | Middle Aged | Young |
| M | 2.84 | 2.64 | 3.44 | 3.56 | .74 | .70 | .76 | 1.12 |
| $s^2$ | 2.91 | 2.93 | 1.31 | 1.50 | .77 | .75 | .43 | .35 |
| $sm^2$ | .0582 | .0586 | .0262 | .0300 | .0154 | .0150 | .0086 | .0070 |
| t | .5853 | | .5061 | | .2294 | | 2.8823** | |

Second

| | Old | Middle Aged | Old | Middle Aged | Old | Middle Aged | Old | Middle Aged |
|---|---|---|---|---|---|---|---|---|
| M | 3.64 | 2.24 | 3.34 | 2.10 | .94 | .42 | 1.30 | .66 |
| $s^2$ | 1.21 | 3.49 | 1.78 | 3.28 | .75 | .58 | .50 | .47 |
| $sm^2$ | .0242 | .0698 | .0356 | .0656 | .0150 | .0116 | .0100 | .0094 |
| t | 4.5662** | | 3.8981** | | 3.1882** | | 4.5944** | |
| | Old | Young | Old | Young | Old | Young | Old | Young |
| M | 3.64 | 2.56 | 3.34 | 2.88 | .94 | .68 | 1.30 | .64 |
| $s^2$ | 1.21 | 2.49 | 1.78 | 2.88 | .75 | .67 | .50 | .48 |
| $sm^2$ | .0242 | .0498 | .0356 | .0576 | .0150 | .0134 | .0100 | .0096 |
| t | 2.5000* | | 1.5067 | | 1.5430 | | 4.7143** | |
| | Middle Aged | Young | Middle Aged | Young | Middle Aged | Young | Middle Aged | Young |
| M | 2.24 | 2.96 | 2.10 | 2.88 | .42 | .68 | .66 | .64 |
| $s^2$ | 3.49 | 2.40 | 3.28 | 2.88 | .58 | .67 | .47 | .48 |
| $sm^2$ | .0698 | .0498 | .0656 | .0576 | .0116 | .0134 | .0094 | .0096 |
| t | 2.0821* | | 2.2222* | | 1.6445 | | .1451 | |

* Significant at .05 level; ** Significant at .01 level.

From the above analyses, it is apparent that age differences emerge as significant most frequently after training. It seems that the after training scores are mainly responsible for the significant *F*'s for age differences in the 4 analyses of variance. However, the same trends are generally evident for the first test.

3) The Water Jars susceptibility scores showed significant age-sex and age-order interactions. Actually, the age-sex interaction may be attributed to an unexpectedly set performance by the younger males. The age-order interaction may be due to the large susceptibility difference between the middle-age groups taking the test first and second. This difference is not paralleled in the other age groups.

4) The Water Jars extinction scores showed significant age-order interaction, a result which

seems attributable to the much smaller set effect after training among the younger subjects. This drop is not evident with older and middle-age groups. The older groups given the Water Jars Test second actually did worse on this score.

*Analysis of intra-group improvement.*—Chi square comparisons were made to indicate the degrees of improvement individuals in each group showed on their second test. Since those who had not shown set on the first measure could not improve and since the meaning of the explanation would not be as definite to them as to the others, for these measures it was decided that only those having maximum set scores on the first test could be compared for relative improvement. The Chi squares indicated significant (.01 level) age group differences in improvement after training on one of the four measures (susceptibility on the Alphabet Mazes when taken after the Water Jars Test). This difference is largely because of the poorer showing of the older group. It may be noted that there is a better chance of showing "improvements" when the Water Jars Test is given first, since it tends to be more set inducing than the Alphabet Mazes Test.

## DISCUSSION

It should be evident that this is not the ultimate study of age differences in problem solving set. Such a study would more successfully yield score differences which were pure and definite measures of set, uncontaminated by operation of extraneous variables. Time, for example, enters into the extinction scores perhaps too heavily. It is difficult to envision a practical test which would not involve some sort of time limit, however, and the meaning of the hindrance effect of set is closely tied to time. In industrial or educational applications, time would seem to be a persistent issue. Older subjects took longer on every phase of the task. This slower speed of work inevitably enters as a contaminating element in the extinction score.

The question may be raised as to whether the older group's showing of more set might be partly attributed to poor memory. They may simply have forgotten the instructions or the training explanation in some cases. This would still constitute a genuine set difference as operationally measured.

The greater improvement with training of the middle-age group may be attributed to superior learning ability, since this sample (and this population) has the highest average education level. If that is the case, the difference is no less real for practical purposes.

Actually, it is debatable whether taking advantage of the shorter solution to "critical problems" is really shorter, or the best way to attack a series of problems. It may be faster to apply the formula which has been working than to stop and consider each new problem in the light of all possible procedures. Decisions take time; one reaches a point of diminishing returns in pausing to consider, compulsively, every conceivable approach before proceeding to a course of action. The more "effective" person in practical affairs seems apt to be more "set" in problem solving. Luchins' clearest argument on the disadvantage of such behavior is in relation to the extinction item, wherein a person may strive ineffectively to solve a simple problem which he has already shown the capacity to work quickly.

A major source of difficulty in interpretation of scores from the tests used was the failure to get enough dispersion. On the susceptibility measures, far too many earned the maximum set score of 4. It would be better to have some means of discriminating among these. If any future studies were to be made with these measures, it would seem advisable to reduce the number of set inducing items.

## SUMMARY

One hundred subjects in each of three age groups (median ages: 66.02, 31.75, and 16.05) were compared for differences in susceptibility to set, ability to surmount set, and trainability in avoiding set. Two tests were used. One was a variation of the Luchins Water Jars Test. The other was an adaptation of an alphabet maze test developed by Cowen and his associates to be comparable to Luchins' test. Half of the subjects in each group were given one test first and half the other. After the first, a standard explanation was given in which the effects of problem solving set were demonstrated and the subject warned to avoid them on the second test.

In 4 analyses of variance, age differences were found to be significant on both susceptibility and surmounting scores for both tests. Analyses of *t*-ratios and the mean trends revealed that on the first test given, the older group showed generally more set on all measures. The middle-age group showed less set and the younger

group least. However, the middle-age group showed least set after training. The older subjects improved least with training. Individual exceptions to all of the group trends were apparent.

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# APPENDIX

## WATER JARS

PAGE 1

In each of the following items imagine you are sent to a large water supply, such as a lake or a well. You may take water from it and pour it back in. You will have water jars with you which hold different amounts and your job is to get a particular amount of water. You do this by pouring back and forth from one jar to another until you have just the amount required, without any guessing.

Here is an example:

1. You have a 4 quart jar, an 8 quart jar, and a 3 quart jar. You are to get exactly 7 quarts.

Answer $4 + 3 = 7$

---

That is, you fill the 4 quart and 3 quart jars and you have exactly 7. You will find this written on your answer sheet in its correct place after the number "1."

Now, try this one:

2. You have jars holding 21 quarts and 4 quarts. Get exactly 13.

PAGE 2

This may seem a little harder but the method is almost the same. You may see that by filling the large 21 quart jar and emptying 4 quarts from it into the small jar you will have 17 quarts left. If you empty that 4 quarts and fill the small jar again you will have exactly 13 quarts left in the big jar. This is written:

Answer $21 - 4 - 4 = 13$

Write this on the line after "2" on your answer sheet.

On the following pages you will find more items of this type. Work each one and mark your answer on the answer sheet provided. *Do not mark this booklet* in any way. You will be given scratch paper for any figuring you may want to do.

As you finish each item, turn the page and *do not turn back* to the item. Once you go on to the next page consider the item done and *do not return to it.*

Do not turn *this* page until told to do so!

PAGE 3

You have jars holding 5 quarts, 12 quarts, and 2 quarts. Get exactly 3 quarts.

5, 12, 2 get 3

PAGE 4
7, 16, 4 get 1

PAGE 5
6, 17, 4 get 3

PAGE 6
9, 16, 3 get 1

PAGE 7
6, 15, 4 get 1

PAGE 8
7, 15, 3 get 2

PAGE 9
8, 19, 3 get 5

PAGE 10
7, 18, 4 get 3

PAGE 11
6, 14, 2 get 4

PAGE 12
7, 16, 2 get 5

PAGE 13

*Stop!*

Wait for signal before turning this page.

PAGE 14
7, 21, 2 get 9

PAGE 15

Now, close the booklet and set it aside. Do not return to any of the items.

## ALPHABET MAZES

PAGE 1

In each of the following items you will see a number of squares. Each square contains a letter of the alphabet. Start with the letter in the **upper right hand corner.** You are allowed to move **one** square at a time in **any direction,** as long as the move helps to spell out a word. Work from one word to another to the finish point so that the last letter of the last word is in the **lower left hand corner.**

In the first sample, on the next page, the path is marked for you. To get from start to finish, follow the letters down the right side, spelling "who." Then go diagonally to spell "is." From there to the finish point is the word "it."

PAGE 2

The whole path, from **start** to finish spells "who is it." You will find this written on your answer sheet in the correct place after number "1."

Now, look at the next sample on the next page.

PAGE 3

It is a little harder, but the method is the same. Just find a path of words from the starting letter to the finish letter at the lower left.

The answer to the second maze is "warm in May." Write this on the line opposite "2" on the answer sheet.

(Go on to the next page.)

PAGE 4

On the following pages you will find more mazes, on which the path has **not** been marked. Work each one and write your answer on the answer sheet provided. **Do not mark this booklet** in any way. All of the solutions will be fairly meaningful phrases. In case there is **more than one path** that will take you from start to finish, the correct solution is the path that uses the **fewest** squares. As you finish each item, turn the page and **do not turn back** to the item. Once you go on to the next page, consider the item done and **do not return to it.**

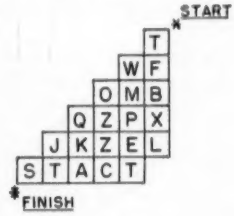
Do not turn **this** page until told to do so!

PAGE 5

PAGE 6

PAGE 7

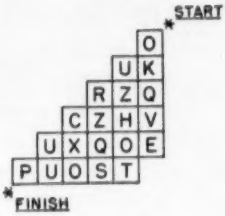
PAGE 8




PAGE 9

PAGE 10

PAGE 11




PAGE 12

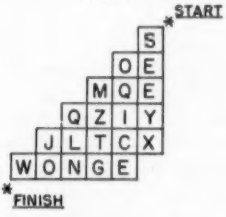
PAGE 13

PAGE 14

PAGE 15

Stop!
Wait for signal before turning this page.

PAGE 16




PAGE 17

Now, close the booklet and put it aside.
Do not return to any of the items.

# AN AGE DIFFICULTY IN SEPARATING SPATIALLY CONTIGUOUS DATA

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This experiment is part of a broad study of complexity in relation to age. It is closely linked with a previously reported experiment (1) in which it was found that difficulty, particularly for older subjects, was associated with increases in the size of the task, although the nature of the problem presented remained essentially the same. The task used in this former experiment required subjects to place numbered counters on a checkerboard in such a way that they added up simultaneously to marginal totals given for the rows and columns. The size of the boards varied from 3 x 3 to 6 x 6 squares, with corresponding increases in the number of counters from 9 to 36. Most of the difficulty experienced by the subjects seemed to be in correcting errors made in the initial placing of counters on the board, which remained when all the squares had been filled. The location of counters incorrectly placed and linking together of them to arrive at a correct solution seemed to cause confusion. It seemed that part, at least, of this confusion was due to difficulty in picking out the relevant counters from among other similar but correctly placed counters, i.e., in treating separately similar items in close spatial proximity. Kay (2), using a different type of task, found what seems to be a similar difficulty which increased strikingly with age. The present experiment was designed to investigate further this aspect of complexity in relation to age.

## METHOD

The task was divided into two parts:

1. *Problem A.* The subject was given a checkerboard (fig. 1) and 14 counters numbered 1, 12 numbered 2, 14 numbered 3, and 10 numbered 4 (total 50) and told to place one counter in each square in such a way that the numbers on the counters would add up to the marginal total given for each row and each column of squares.

When the subject had completed this task, the counters were re-stacked and the board replaced by another in full view of the subject.

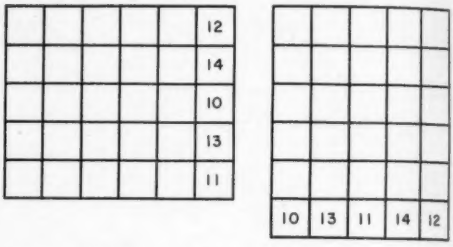


Fig. 1. Checkerboards used in Problem A.

2. *Problem B.* The subject was then told to carry out the same task as before, but to note that this time each square was divided into halves (fig. 2). He was instructed to place counters in the upper halves of the squares to add up to the totals given for the rows, and in the lower halves to add up the totals given for the columns.*

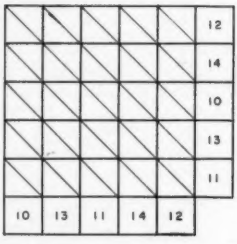


Fig. 2. Checkerboard used in Problem B.

The boards were made of white cardboard. In Problem A the squares were formed by horizontal and vertical black lines 3.5 cm. apart. In Problem B the squares were formed by lines drawn 5.5 cm. apart, and each square was divided by a diagonal line. The white ivorine counters were 2.8 cm. in diameter, and a number, 1.3 cm. high, was engraved in black on each.

Submitted for publication December 8, 1955.

Acknowledgment is made to Mr. L. V. Green and the Dunlop Rubber Company, who kindly provided facilities for testing, to their employees who took part in the experiment, to all the others who kindly acted as subjects, and to Mr. A. T. Welford, Director of the Unit, for his valuable suggestions and criticism throughout.

* In a pilot experiment, subjects of all ages were asked to choose on which side of the diagonal they preferred to place the counters for rows, and the majority chose the upper half.

TABLE 1. DISTRIBUTION OF SUBJECTS ACCORDING TO NUMBER OF INCORRECT MARGINAL TOTALS. MEAN AGES ARE GIVEN FOR ALL GROUPS.

| Number of Incorrect Marginal Totals | Age Groups | | | | | | | | | | | | Totals | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20+ | | 30+ | | 40+ | | 50+ | | 60+ | | 70+ | | | |
| | A | B | A | B | A | B | A | B | A | B | A | B | A | B |
| 0 | 13 | 15 | 10 | 10 | 10 | 7 | 10 | 8 | 9 | 6 | 8 | 5 | 60 | 51 |
| 2 | 2 | .. | .. | .. | .. | 1 | 1 | 3 | .. | 2 | .. | .. | 3 | 6 |
| 3 | .. | .. | .. | .. | .. | 1 | .. | .. | .. | 1 | .. | .. | .. | 2 |
| 4 | .. | .. | .. | .. | 1 | 1 | .. | 2 | .. | .. | .. | 2 | 1 | 5 |
| 5 | .. | .. | .. | .. | .. | .. | 1 | .. | .. | .. | .. | .. | 1 | .. |
| 6 | .. | .. | .. | .. | .. | 1 | 1 | .. | .. | .. | .. | .. | 1 | 1 |
| 7 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 1 | .. | 1 |
| Mean age | 23.0 | | 33.9 | | 45.3 | | 56.6 | | 65.0 | | 72.4 | | | |

Sixty-six subjects were tested. Their ages ranged from the twenties to the seventies (table 1). They consisted of skilled industrial workers and junior management, police, university laboratory assistants and technicians. These persons are all commonly regarded as of approximately the same occupational status in that they are included under the British Census classification 3. Some of the subjects in their twenties were naval ratings, who by educational and social background would fall into the same class.

## RESULTS

*Problem A.* This problem was clearly well within the average capabilities of all the age groups tested. Only 6 subjects failed to carry out the task successfully (table 1), and although there was some rise with age as far as the forties in times taken this was not significant (table 2).

*Problem B.* A significant increase with age in the number of unsuccessful subjects ($P<0.01$; table 1) was accompanied by a significant rise

TABLE 2. DISTRIBUTION OF SUBJECTS ACCORDING TO TIMES TAKEN AND THE MEAN TIMES FOR EACH AGE GROUP.

| Seconds | Age Groups | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20+ | | 30+ | | 40+ | | 50+ | | 60+ | | 70+ | |
| | A | B | A | B | A | B | A | B | A | B | A | B |
| Under 120 | .. | 1 | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| 121–240 | 6 | 5 | 3 | 3 | 5 | 3 | 2 | 2 | 1 | 2 | .. | 1 |
| 241–480 | 9 | 7 | 6 | 5 | 4 | 7 | 10 | 2 | 6 | 6 | 6 | 5 |
| 481–960 | .. | 2 | 1 | 2 | 1 | 1 | 1 | 7 | 2 | .. | 2 | 1 |
| Over 960 | .. | .. | .. | .. | 1 | .. | .. | 2 | 1 | 1 | .. | 1 |
| Mean Time: | | | | | | | | | | | | |
| Problem A | 294 | | 366 | | 405 | | 385 | | 382 | | 407 | |
| Problem B | 286 | | 336 | | 329 | | 636 | | 413 | | 522 | |

with age in times taken ($P<0.01$; table 2). Most of this was due to the substantial increase in times taken by the fifties' group compared to the younger groups, although both the sixties and seventies were slower on the problem than the under-50 groups.

It seemed fairly clear that Problem B became relatively more difficult than Problem A with increase in age. To provide a further check the differences of the errors made by each subject on the two problems were tabulated (results shown in table 3). The increase of error with age is significant ($P<0.05$) and the trend is clear except for the two subjects in the fifties who improved their performance. These two subjects did not, perhaps, go against the trend as much as would at first appear, because the fifties were the most inaccurate group of all on Problem A, and thus had more scope for improvement than the others. While they showed this improvement, neither of the two subjects completed Problem B correctly. We may also note that the fifties were the only group showing a significant increase of time taken on the second problem. The trend would probably have been clearer had it been possible to combine time and accuracy into a single score. As it is, taking time and accuracy together, the twenties and thirties improved slightly in both respects on Problem B; the forties were quicker but less accurate; the fifties took longer time for about equal accuracy; and the sixties and seventies on average were both less accurate and took longer time.

An analysis of the strategies adopted by the subjects suggested that their methods may be divided into three groups:

(a) One set of totals, either rows or columns, is completed before the other is started.

(b) Rows and columns are worked together, either according to a spatial pattern or to corresponding marginal totals.

(c) The counters are selected according to value, e.g., all the 4's first, and arranged in either rows or columns or both together. While this method overlaps the other two, it represents an attempt to deal with the problem as a whole, rather than as a series of sub-totals.

The only noticeable tendency with age to use one strategy rather than another was that of the 5 subjects on Problem A and 7 on Problem B who adopted the third method, only 1 was over 50. Fifty-seven of the subjects adopted the first strategy for Problem A, all but 2 of them completing rows before columns. Of the 21 subjects who altered their method when faced with Problem B, 17 changed from the first to the second method, as compared to 4 who changed in the opposite direction. It is doubtful how far this may have contributed to the older subjects' difficulty with Problem B: slightly more older than younger subjects altered their methods on Problem B ($P<0.1$), and those who adopted a new strategy for Problem B tended to spend longer on it than they had done on the first problem ($P<0.1$).

Differences between the two problems were observed, however, in the ease with which these methods were carried out. The subjects had no difficulty in maintaining their initial strategy on Problem A. The subjects in the over-40 groups

TABLE 3. COMPARISON OF ACCURACY ON PROBLEMS A AND B.

| Number of Correct Marginal Totals on Problem A Minus Those on Problem B | Age Groups | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 20+ | 30+ | 40+ | 50+ | 60+ | 70+ | |
| −4 | .. | .. | .. | 1 | .. | .. | 1 |
| −3 | .. | .. | .. | .. | .. | .. | .. |
| −2 | 2 | .. | .. | .. | .. | .. | 2 |
| −1 | .. | .. | .. | 1 | .. | .. | 1 |
| 0 | 13 | 10 | 8 | 9 | 6 | 5 | 51 |
| +1 | .. | .. | .. | .. | .. | .. | .. |
| +2 | .. | .. | 1 | 1 | 2 | .. | 4 |
| +3 | .. | .. | 1 | .. | 1 | .. | 2 |
| +4 | .. | .. | 1 | 1 | .. | 2 | 4 |
| +5 | .. | .. | .. | .. | .. | .. | .. |
| +6 | .. | .. | .. | .. | .. | 1 | 1 |

became confused and had difficulty in keeping the two blocks of squares separate on Problem B. Their comments made it clear that they understood the instructions before they began, but they seemed to forget them as they went on. Some added the counters in the upper halves of the squares to equal a column total instead of a row total. Others added up both sets of counters to equal the same total. Several were observed to take a counter from a correct row to correct for an error in a column, or vice versa, because it was the nearest counter of the required value, and to replace it with another counter without any regard to the effect the exchange would have on the previously correct total. Several said they found the display of Problem B much more confusing than that of Problem A, and it seems clear that this resulted from having counters referring to both rows and columns in the same square. Some subjects had difficulty in locating a second incorrect row or column when faced with one incorrect total, and when trying to find it sometimes forgot where they had found the original error. One remarked: "I can't find it, but I'm only looking down not across." Another remark, "If only I could remember where there is one too many," indicates that the subject found it difficult to hold certain facts in mind while looking for other errors.

The errors remaining in the solutions seemed to indicate that this difficulty was common. Only 6 of the incorrect solutions contained errors which could be corrected by a direct exchange of two counters. The remaining 15 would have involved a more elaborate series of moves, each achieving a part correction before the error was eliminated. A few of the subjects who attempted such a series of moves seemed to "lose the thread" of what they were trying to do when part way through. It may have been anticipation of this that led several of the older subjects to prefer to leave errors in their solution of Problem B, recognizing they had left them, rather than to attempt a rearrangement of the counters.

Many of the younger subjects, but few of the older, checked each total as they completed it, and corrected any errors they had made before starting the next.

Several older subjects made use of verbal cues as an aid to memory. For instance, one subject completed all the rows on Problem B and looked at each column total before placing a counter in it, saying "Now 10," and then, "Now 13," and so on.

## DISCUSSION

The differences between the performances on the two problems and their relation to age are remarkable in view of the fact that all the subjects completed Problem A first and that Problem B was in essence identical with it. The two younger groups gave performances on Problem B consistent with learning having taken place. Many subjects in the over-40 groups, however, found the second problem far more difficult than the first. Some of them began to have difficulty when about half the counters were on the board, and made errors of addition. By the time they had placed all the counters, they were quite confused and unable to keep the rows and columns of counters separate in order to carry out corrections. This was true in spite of every indication that the subjects' interest was well maintained; for instance, several who gave up before completing Problem B, made notes of the details of the problem to continue work on it at home.

Problem A provides a control for a previous experiment (1) in which counters had to be arranged on a checker board so that the same counters added up to marginal totals on both rows and columns. Under these conditions, subjects in their sixties and seventies made, on average, substantially more errors than those in their twenties, with problems using 5 x 5 or 6 x 6 checker boards. The fact that no such fall of performance with age appeared on Problem A indicates that when the two dimensions are separated the difficulty largely disappears.

The results for Problem B are similar to those of the earlier experiment in that there is no straightforward relationship between times taken, errors made, and age. While it may perhaps be true that had the unsuccessful subjects in their forties spent longer on the task they would have been successful, as were those in their fifties, it cannot be assumed that this would also apply to the over-60 groups. In the previous experiment, it was found that time was associated with success on a moderately difficult task, but that additional time did not insure success on the very difficult tasks. In fact, the longer the older subjects spent on the latter the more confused they became. They appeared to realize this quickly and to be content with a lower standard of performance.

The practical implications from these results are that older people are able to organize a large number of items presented at one time equally as well as younger people, provided that the display enables them to keep related items spatially distinct from similar but unrelated material. When this is not possible, older people may be at a considerable disadvantage.

## SUMMARY

The task of arranging 50 numbered counters in 5 rows and 5 columns of squares to add up to the marginal total printed for each on a checker board was given under two display conditions to 66 subjects, whose ages ranged from the twenties to the seventies. The task was carried out correctly by almost all subjects when the rows and columns were clearly separated in the display. When the task was presented for the second time under conditions in which the two sets of squares for rows and columns overlapped, there was a significant decline in accuracy with age, accompanied by a rise in time taken. Some of the older subjects seemed to have difficulty in separating relevant from irrelevant, but similar, items in close proximity.

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# THE EFFECT OF MIGRATION ON THE NUMBER AND DISTRIBUTION OF THE AGED IN FLORIDA

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Although it is generally recognized by demographers that older people are the least migratory of all age groups (4, 9), it is known also that in recent decades there has been a considerable interstate movement of elderly persons (2). This stream of migration has flowed mainly from the Northeast and North Central Regions to states on the Gulf and Pacific coasts.

The movement of large numbers and proportions of persons in the older ages into a few states which are made attractive by their mild climate and by other factors has importance from a number of points of view. Basically, the migration necessitates personal readjustments on the part of the older people who move and social readjustments on the part of the communities in which they take up residence. These readjustments have social, economic, and political aspects. Moreover, a relatively heavy influx of the aged may change, to a greater or lesser extent, the ethos or distinguishing cultural patterns of a community.

Earlier studies (13) have suggested that older migrants to Florida have settled in disproportionate numbers in certain sections of the state. The purpose of the present investigation is to measure, as accurately as the data permit, the volume and relative importance of movements into the state and its 67 counties during the decade ending in 1950.

## METHOD

Official census data do not lend themselves to the direct determination of the size and direction of streams of migration during 1940-1950. Accordingly a technique employed earlier by Smith (5, 6, 7, 8) and Hitt (3, 4) has been utilized to obtain presumptive evidence. The method involves the following computations:

1) The population aged 55 and over on April 1, 1940, when the sixteenth census was taken. This population should comprise, when allowance for mortality has been made and in the absence of migration, the group aged 65 and over in 1950.

2) The expected population aged 65 and over in 1950. The assumption is made that mortality in the state and its counties is the same as that in the nation. For the whole aged population the rate of attrition between 1940 and 1950 was 37.4 per cent; for the white population, 37.6 per cent; for the Negro 34.5 per cent.

3) The population aged 65 and over actually enumerated on April 1, 1950.

4) The difference between the expected and the enumerated population. It is assumed that this figure represents net gain or loss due to migration between the two census dates of persons who were 65 years of age in 1950.

## RESULTS

*Absolute Changes, 1940-1950.*—The application of the above procedure to the census data (10, 11) indicates that Florida had, in 1950, 66,484 more elderly residents than would have been the case had there been no migration. The vast majority of these persons were white. The net increase due to migration of 2,655 Negroes represented only 4.0 per cent of the gain in total aged population experienced by the state. Since the movement of white persons so far overshadows the incoming stream of nonwhites, the results are presented only on the basis of race, a procedure which permits a more discriminating analysis.

Fifty-four of the state's 67 counties gained older white people as a result of migration during the decade. However, in 15 counties the increases amounted to less than 100 persons. To lessen the possibility that errors in enumeration or other factors will influence the findings, only the 39 counties in which the net increase was 100 or more white persons aged 65 or over in 1950 are considered for further analysis.

Pinellas County, in which the well-known retirement city of St. Petersburg is located, experienced by far the largest gain through migration, 15,290 persons. Dade County (Miami)

Submitted for publication February 16, 1956.
Presented at the annual meeting of the American Sociological Society, Washington, D. C., September 2, 1955.
Published on a grant from the Forest Park Foundation to the Journal of Gerontology.

was next, with 12,853 more aged residents attributable to migration. Both of these counties were in a class of their own with respect to net gains due to migration. As the accompanying figure indicates, 3 other counties realized increases in excess of 3,000. These are Orange (Orlando), 4,427, Hillsborough (Tampa), 3,720, and Palm Beach (West Palm Beach), 3,190.

In 7 other counties, from 1,000 to 3,000 more aged white residents than would have been found in the absence of migration were counted. These were Broward (Ft. Lauderdale), Duval (Jacksonville), Lake (Leesburg), Manatee (Bradenton), Polk (Lakeland), Sarasota, (Sarasota), and Volusia (Daytona Beach).

Although 13 counties are shown by the method used to have lost older white residents during the decade, none decreased by as many as 100 persons. The largest decrease was that of Gilchrist County, a jurisdiction without urban population according to the census definition, in which the loss was only 53 persons. Since these net decreases were so small, they merit no detailed consideration.

Of the 38 counties which gained elderly Negro residents during the decade, only 13 had increases of 100 or more persons. Four counties were the recipients of from 200 to 450 migrants: Duval, 444, Polk, 316, Hillsborough, 219, and Pinellas, 200. The 9 other counties whose gains supposedly due to migration fell between 100 and 200 were Alachua (Gainesville), Bay (Panama City), Broward, Dade, Escambia (Pensacola), Leon (Tallahassee), Orange, Palm Beach, and Seminole (Sanford).

As in the case of the aged white population, no one county in the state lost as many as 100 elderly Negroes during the decade. Twenty-seven counties sustained slight losses, the largest being that of Monroe (69 persons).

*Relative Changes, 1940-50.*—The magnitude of gains or losses due to migration may be assessed by relating the enumerated population aged 65 and over in 1950 to the expected population as computed. For the aged population of the state, the ratio of enumerated to expected population was 138.9; for the white aged, it was 144.7; and for the Negro aged, 108.5. In the discussion which follows, only those counties which experienced a net gain of 100 or more persons putatively through migration are considered.

For the white population there were 39 counties for which the ratios were in excess of 100. Twenty-six of these had ratios of 125 or above, indicating that one-fifth or more of the older persons counted by the Census Bureau in 1950 had migrated into the county during the preceding decade.

Pinellas County, in which the ratio of actual to expected population was 212.3, ranked all other counties in the state. Only one other county, Sarasota (210.3), owed more than half of its 1950 aged white population to migration during the 10-year period.

In 11 counties ratios were between 150 and 199: Broward, 193.4; Orange, 169.2; Manatee, 169.0; St. Lucie, 161.9; Highlands, 160.1; Osceola, 159.1; Brevard, 157.1; Dade, 155.6; Clay, 153.1; Palm Beach, 152.9; and Charlotte, 150.5.

Relative gains in the aged Negro population of the counties were decidedly lower than those for the white population. Bay County, with a ratio of 147.9, far outdistanced the others. Polk, for which the ratio was 130.3, was next. The only other counties for which ratios were higher than 120 were Broward and Pinellas, in both of which the increase due to migration during the decade amounted to 124.1.

## DISCUSSION

The available evidence indicates that two states, California and Florida, have during the last two decades received the largest numbers of aged migrants. Smith (8) has calculated that in 1940 California had 57,000 residents and Florida 33,000 residents aged 65 and over who had moved into the state during the preceding decade. The comparable figures for other states which received a substantial number of older migrants during the 1930-1940 decade are: Texas, 21,300 Tennessee, 8,676; Louisiana, 8,076; Mississippi, 7,535; Washington, 7,115; Oklahoma, 6,913; Missouri, 4,413; Minnesota, 4,419; and Oregon, 3,875.

Using a similar method, Hitt (4) found that from 1940 to 1950 migration accounted for the movement of 130,000 persons into California and 66,000 persons into Florida who were 65 and over on April 1, 1950. Other states which realized fairly large increases in their aged populations due to migration during the most recent intercensal period are Texas (32,000), Washington and Louisiana (12,000), Arizona (8,900), Alabama (8,100), and Oregon (7,000).

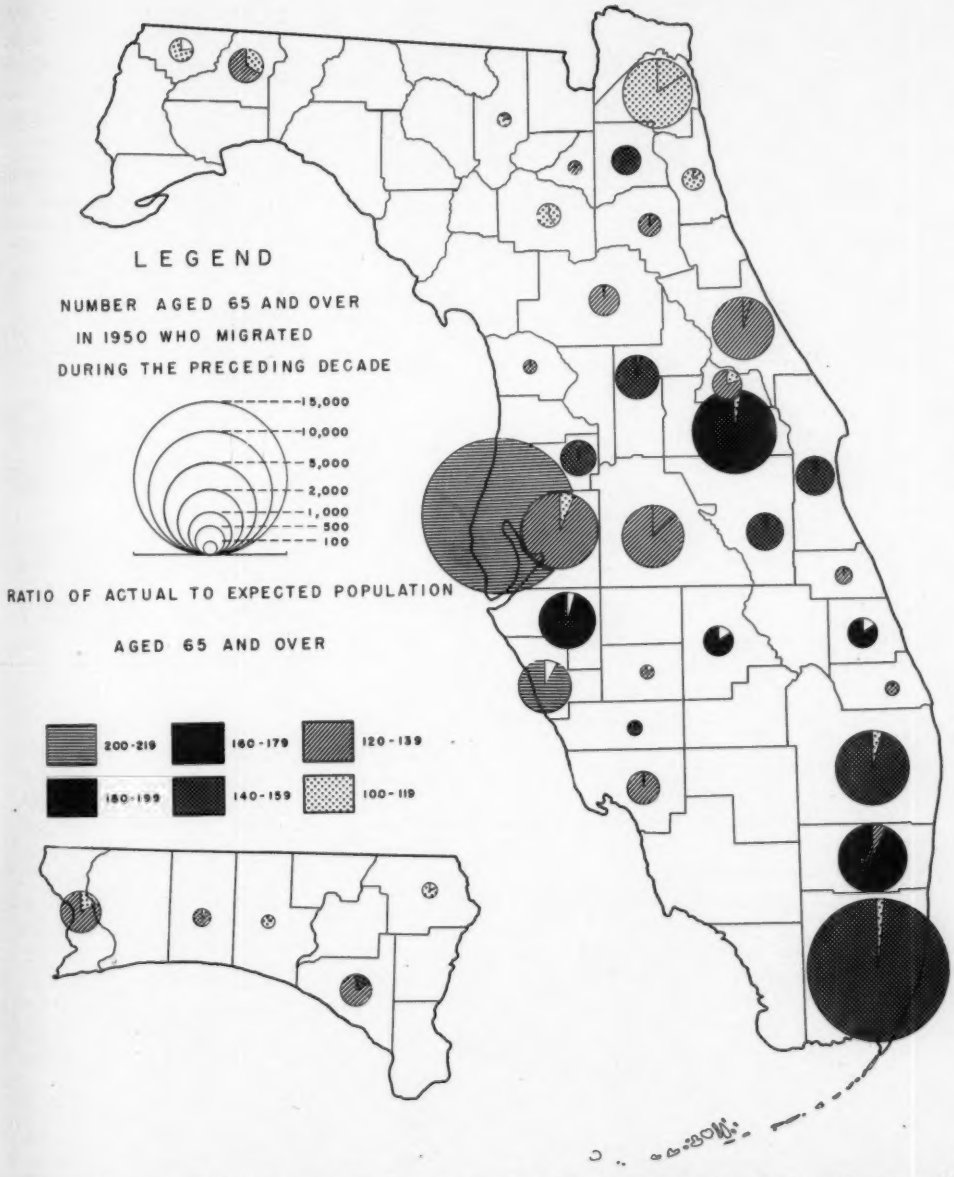


Fig. 1. Number and relative importance of aged migrants to Florida, 1940-1950, by County. (Starting at 12 o'clock on the circles and reading clockwise, the first segment represents Negro migrants and the second white migrants. For method and sources of data, see text.)

The states which lost older residents in the greatest numbers between 1930 and 1940 were Pennsylvania (33,239), New York (25,800), Illinois (12,780), New Jersey (11,370), Indiana (10,597), Massachusetts (10,139), and Ohio (9,702). Those which sustained the heaviest losses of older persons between 1940 and 1950 (4) were New York (55,900), Pennsylvania (52,500), Illinois (31,200), Ohio (15,800), Massachusetts (14,400), Iowa (13,300), Indiana (12,600), Missouri (11,000), and Minnesota (10,000).

These gains and losses take on greater significance when they are related to the aged population that would have been found in the various states had there been no migration. In this respect Florida was a special case; its increase between 1930 and 1940 of persons who were 65 years old or over in 1940 amounted to 25.1 per cent of all persons in that age group on the census date. California, the state in which migrants constituted the next highest share, had gained 10.3 per cent of its elderly residents during the preceding decade (8). Migration between 1940 and 1950 accounted for 28.0 per cent of the older inhabitants of Florida and for 14.6 per cent of those living in California on the census day in the latter year (computed from data in reference 12).

It is well established that large numbers of white persons have migrated to Florida subsequent to retirement. It is usually assumed, on the other hand, that Negroes have not shared in this movement in appreciable numbers. This notion is based in part on the existence in the state of the traditional majority-minority social structure of the South, which is believed to make it unattractive to members of nonwhite races, and it is reinforced by the absence of noticeable facilities for nonwhite retired persons. The state census conducted in 1945 demonstrated that only one nonsouthern state, New York, was the birthplace of as many as 1,000 of the 28,096 Negroes then residing in the state (1). In the light of the state census data, it seems likely that most of the older Negro migrants who arrived in the state during the decade under consideration originated in nearby states, notably Georgia, Alabama, and South Carolina.

It should be observed also that the procedure followed in gauging the amount of migration combines intercounty and interstate movements. It is possible that intercounty, especially rural-urban migration is of particular significance in the case of older Negroes.

The results presented above indicate that with respect to numbers of white persons the largest increments went during the decade in question to areas located in the peninsular section of Florida; all except one (Orange) of the counties involved are situated on the Gulf of Mexico or the Atlantic Ocean. The 5 counties which gained 3,000 or more migrants are found in central and southern Florida. Only one county in northern Florida, Duval, gained as many as 1,000 new elderly residents. Moreover, all counties whose increases were over 1,000 older white persons were areas of rapid growth, none having gained less than 33.0 per cent of its population during the decade.

Both of the counties (Pinellas and Sarasota) which more than doubled their expected aged white populations are located on the Gulf in the west-central part of the peninsula and both experienced extremely rapid growth of their total populations during the decade being reviewed. Pinellas' and Sarasota's over-all increases of 73.4 and 79.0 per cent, respectively, were far above the state's gain of a 46.1 per cent. All counties for which the ratio of enumerated to expected elderly population ranged between 150 and 199 lie in the peninsula, only one (Clay) being located in the northern part of the area. Eleven of the 13 counties with highest proportional increases of older people experienced substantial rates of increase for their total populations, ranging from 33.0 to 121.4 per cent during the decade. The two exceptions were Charlotte County and Osceola County, in which the gains in population were 17.0 and 12.7 per cent respectively. Charlotte is notable for having had 14.7 per cent of its people in the 65-and-over category at the time of the 1950 census. Osceola County, in which 21.6 per cent of the residents were aged at that time, includes the small city of St. Cloud, which had 41.6 per cent of its people in the older classification.

Gains in population as a result of migration of aged Negroes were much smaller in numbers and affected few counties. Three of the 4 counties which received from 200 to 450 elderly Negroes—Pinellas, Hillsborough, and Polk—are contiguous, lying in the west-central part of the peninsula. Duval County, which registered the greatest increase of nonwhites through migration (444), is found in the extreme northeast

portion of the state and is well known as the mecca of many migrants of both races from nearby areas in Florida and from contiguous states. None of these 4 counties increased its total population less than 38.7 per cent during the decade. The 9 counties in which increases of aged Negroes ranged between 100 and 199 are found in what is usually known as West Florida as well as in the central and southern parts of the state. Each grew rapidly (from 20.5 per cent to 110.9 per cent) during the 10-year period.

The relative increase of elderly Negroes through population movement was much less striking than that of the white population. In no county was the ratio of actual aged population to expected aged population as high as 150. For Bay, in the panhandle of the state, the ratio was 147.9; for Polk, near the center of the peninsula, it was 130.3. Bay County, situated on the Gulf, grew at the rate of 106.4 per cent between 1940 and 1950; Polk, an inland county, increased 43.1 per cent. Migration in the 11 other counties which received 100 or more elderly persons during the decade was in no case of large proportions.

If the technique used in measuring migration of the elderly produces valid results, the volume of the movement into Florida between 1940 and 1950 was nearly double that of the immediately preceding decade. Various evidence which cannot be detailed here suggests that this movement has proceeded at an increasing rate since 1950. It would seem, therefore, that certain parts of the state which are favored by retired people because of mild climate, accessibility to coasts, housing, and recreation facilities, and the institutionalization of the status of retired person will continue to realize larger increases, absolutely and relatively, in the aged part of their population.

## SUMMARY

Census data have been analyzed for the purpose of ascertaining the number of elderly persons who migrated to and from Florida counties during the decade ending in 1950 and the relative importance of these migrants in terms of the numbers of aged persons expected to survive on the basis of the national mortality experience. A large proportion (96.0 per cent) of the 66,500 aged migrants to the state were white. Counties which gained the largest numbers of older white persons are found in the central and southeastern parts of the peninsula. Those which had the largest proportional increases are located in the west-central portion of the peninsula. In general, counties in the panhandle and in the northernmost part of the peninsula did not experience large absolute or relative gains of older white persons. Migration of aged Negroes to Florida counties was relatively small in volume and affected few counties to the extent of gains of 100 or more persons. With minor exceptions those counties which received the largest volume of migrants, absolutely and relatively, of either or both races, had high rates of growth for the total population during the decade and were located on seacoasts. No county lost as many as 100 aged persons—total, white, or Negro—due to migration during the 10-year period.

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# THE ROLE OF WELFARE AGENCIES IN PROVIDING SERVICES TO THE AGED: THE ROLE OF THE PUBLIC AGENCY

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The role of the Federal welfare agency in encouraging, maintaining, and extending the services of state and local welfare agencies to aged persons is only one aspect of the Federal Government's attempt to assist aged persons but a very vital one and one which will grow in importance. For the past 20 years the Federal Government's role in this respect has been one of trying to meet the basic income needs. At the present time some 6 million aged persons are receiving monthly old age insurance payments and 2.5 millions are receiving monthly old age assistance payments. There necessarily has been a preoccupation at the Federal level with income-maintenance and only recently has major emphasis been given to how services to the aged can be greatly accelerated.

State and local public welfare agencies and private agencies are providing a wide range of services to older people. Moreover, the activities of these agencies have been growing in order to meet the need arising from the increase in older persons in our population. The Federal Government, however, can aid materially in this by making a number of changes in emphasis in the Federal program. These are:

1.) Earmarking Federal funds for medical care for old age assistance so as to encourage additional funds for all types of medical and nursing home care of older people, making available more adequate medical care to all aged persons on the assistance rolls.

2.) Modifying the old age assistance provisions of the Social Security Act to make clear that one of its objectives is to restore aged persons to self-support and self-care. Clarification of Federal objectives would not only encourage the use of state and Federal administrative funds for this purpose but would also provide greater incentive for state program development in providing services to older people both by the public assistance agency and through the maximum utilization of other agencies offering similar or related services.

3.) Authorizing Federal funds for the training of state and local welfare workers not only to provide social services but also to encourage community provision of services to older people.

4.) Authorizing use of Federal funds for demonstration and research projects of a national, regional, or state significance.

## MEDICAL SERVICES FOR OLD AGE RECIPIENTS

Old age assistance recipients are, on the average, about 75 years old. Their age, income level, physical status, and previous environmental conditions all indicate the need for more than the average hospitalization, nursing care, and other medical services. Existing arrangements in many places are clearly inadequate to provide the quality and quantity of medical services which the aged require. Voluntary insurance is nonexistent for the assistance group. There is a wide range in what is now available in medical services to aged persons; this variation in services and the wide variation in costs indicates that much more can and should be done to make medical services in some states and localities more generally available to aged persons on the assistance roles. More and better nursing homes, specialized services for the chronically ill, trained personnel in the whole evolving field of geriatrics, the development and coordination of community health services in relation to adult education, recreation and rehabilitation, and adequate guardianship provisions are needed.

The existing Federal formula providing grants for public assistance has not provided the necessary flexibility or sufficient incentive for the states to develop adequate medical care programs for assistance recipients. The President has recommended to Congress, therefore, that each of the public assistance titles in the Social Security Act be amended to provide separately earmarked financing of the medical care costs of assistance recipients. It is esti-

Presented at the Eighth Annual Scientific Meeting of the Gerontological Society, Sheraton-Belvedere Hotel, Baltimore, Maryland, October 29, 1955.

Published on a grant from the Forest Park Foundation to the Journal of Gerontology.

mated that, under the President's proposal, total medical care expenditures (Federal, state, and local) for public assistance recipients in the 4 Federally-aided categories would increase from the present $220 million a year to about $335 million a year. Thus, there would be a 50 per cent increase in medical care expenditures for assistance recipients in the 4 Federally-aided categories. While there would still be inadequacies in some areas, a change in the program to provide more adequate medical services would be an important step in the direction of meeting one of the most pressing needs of old age recipients.

### SELF-SUPPORT AND SELF-CARE

Many persons on the old age assistance rolls have potentialities which are not being utilized. Idleness and loss of companionship may hasten the aging process by accelerating physical and mental deterioration. Many old age assistance recipients believe they are unwanted and have been pushed out of the stream of life. They are moved out of responsibility in religious or voluntary organizations.

Social withdrawal is induced as much by these circumstances as by sickness, widowhood, and reduced income; so are moodiness and depression, irritability, and submission. Senility comes to few older people, but the irritability, confusion, forgetfulness, and repetition, which are mistaken for it, come to many when living is complicated by inadequate income, loneliness, inactivity and frustration. Some find outlets in phantasies and in hallucinations and in regression to infancy; others suffer from loss of sight, hearing, and memory. Constant complaints are common characteristics of older persons whose needs are not being satisfied.

It is impossible to escape the conclusion that loss of useful roles in work and in the family is responsible for much of the boredom, frustration, confusion, unhappiness, and premature aging among today's aged. Declining health, insufficient income, and loss of the marriage partner are, of course, contributing factors.

To begin to overcome some of these difficulties, we have recommended that the legislation providing Federal grants to the states for old age assistance clearly spell out that services for self-support and self-care are one of the objectives of the program and that Federal and state funds may be properly used for this purpose. We would hope to strengthen and expand by this means the activities of state and local welfare departments in the direction of providing a wide and constructive range of services for older persons on the assistance rolls.

### TRAINING OF PERSONNEL

This proposal is closely related with the third suggestion made to authorize the use of Federal funds for the training of public welfare personnel. There are nearly 6 million persons receiving assistance from public welfare agencies at the present time and there are not enough trained personnel to handle all the many complex human problems faced by the welfare departments in the exercise of their responsibilities.

Every state agency and every important local welfare agency should have on its staff persons primarily concerned with the welfare of older persons. There is not sufficient personnel to do the job, and it is necessary that persons be trained for this responsibility. The Federal Government has a role to play in encouraging the training of personnel for this purpose, working with the schools of social work, public administration, public health in the development of appropriate courses; in in-service training courses, institutes, and seminars; in establishing traineeships and fellowships.

### DEMONSTRATION AND RESEARCH PROJECTS

To round out this picture some funds should be allocated for specific demonstration projects to show how particular methods, ideas, or new emphases work out in practice. The best evidence of the great value of the demonstration approach is that which took place in the children's health and welfare fields during the past 20 years. With a modest amount of money much can be done to stimulate local and state action by showing what works, by eliciting the support of local people and finding out what difficulties must be overcome, by showing a specific result to the taxpayers, the newspapers, and the experts.

Social and economic research should not be forgotten, research designed to point up in local areas and in the states the problems which lie ahead, the ways in which people work, live, and play, their incomes, needs, resources, and how programs have worked out in practice.

SUMMARY

Social security and related programs are providing $6.5 billion a year in income to aged persons. This figure will grow as our social security program matures. The income of all aged persons in the United States is estimated at about $20 billion a year, and this total can be expected to increase. The growth of income maintenance plans for the aged has made it possible for both public and private agencies to begin to give greater consideration to more effective ways and means of improving services to older people.

It is from the experience, resourcefulness, and wisdom of the individual in his membership in the family and the community that our society finds the dynamics of continued development. Old age security consists of both a regular income and reinforcing the value of the older person as a human being with a mind and a spirit as a member of the family and the community.

State and local public welfare agencies are located in every county of the United States and often are the only social agency in some areas. In the past 20 years they have developed a wide range of services to all segments of the population. State and local public welfare agencies must play an ever greater role in providing services to older people. The Federal Government can aid the states in carrying out their basic responsibility not only through financial aid but through offering technical consultation and information on program developments.

The Federal-state partnership has been a cooperative one. This partnership can be broadened to give greater emphasis to the service aspect.

# AGE AND ACHIEVEMENT: A CRITIQUE

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The recent book by Lehman (1), *Age and Achievement*, seems to indicate that in many fields relatively little creative work of importance is done by persons past 45 or 50 years of age. This generalization does not hold in all fields of creativity, but the preceding sentence expresses Lehman's most striking finding.

That the production of first-rate work in poetry, art, science, and other creative areas decreases markedly with age is a matter of prime importance. If correct, it suggests that the creative worker in many fields should plan for early superannuation. If the conclusion drawn by Lehman is erroneous, the impression which it has created should be corrected with dispatch, for a conviction that early deterioration is inevitable may itself have deleterious consequences. Clearly the relationship of age to achievement is a topic in regard to which conclusions should be drawn with extreme care.

It is the thesis of this paper that much of the apparent decline in creative achievement revealed by Lehman's tables and graphs is due to factors other than age. We believe Lehman's data give a spurious appearance of age decrement in creativity.

Let us note first that the studies presented by Lehman are so numerous and so varied that it is difficult to do justice to them in a brief recapitulation. However, it is not incorrect to say that Lehman has been interested primarily in determining the 5 or 10 year age-period in which important creative works have most often been produced. The first step in his procedure, typically, consists in identifying important works in some field. To avoid introducing a bias of his own, he always uses a list of works drawn up by some other person. Lehman then determines the age at which each item was produced. He has done this for many creative fields, including mathematical discoveries, contributions to chemistry, lyric poems, and operas, to mention only a few. The first six chapters of his book are devoted to presenting the results of these analyses.

The graphs in these chapters almost all indicate that the production of outstanding works rises to a peak relatively early in the adult years and then declines. The age at which the peak of productivity is reached varies from field to field. It is as early as ages 22-26 for lyrics, ballads, and odes, and as late at 40-45 for novels, metaphysics, and miscellaneous prose writings. However, for a considerable number of fields the top rates for the production of outstanding works occur between ages 30 and 39.

Many aspects of these curves are worthy of attention, but we are concerned chiefly with the decrements which follow the peaks. In most instances, as presented by Lehman, the decrements are very striking. For example, (p. 5) at ages 40-45 chemists produce, per man, only one half as many significant contributions as they produce between ages 30-35. By ages 60-65 their rate of production is only 20 per cent of their peak rate. Other graphs give very similar data for other sciences. The fine arts also show a severe decrement. For example, (p. 60) by ages 45-50 the production of orchestral music judged to be of highest merit is only about 40 per cent as great as it was 10 years earlier. By ages 55-60 the composition of orchestral music of high quality decreases to 20 per cent of the maximum rate.

Examination of such findings, page after page, creates an impression of inevitable decline. If these charts are taken at their face value, we must conclude that in most kinds of creative work the output of work of first-rate quality is greatly reduced after the thirties.

But should these charts be taken at their face value? Let us consider this question.

A major methodologic weakness in Lehman's treatment of data lies in the fact that in most instances a table or graph combines information pertaining to men of different degrees of longevity. Thus a table usually presents data for men nearly all of whom reached age 30, but only part of whom attained age 40, and still fewer of whom completed half a century of life. To equate for differences in numbers of subjects at different ages, Lehman found the mean number of important contributions per person for persons surviving each decade. We shall attempt to show that this method of treating data acts in part to produce the productivity differentials which Lehman discovers.

Let it be noted that each man whose record is used by Lehman is required to produce only one important work in order to qualify for inclusion. In most lists of outstanding works used by Lehman, each individual contributes one, or only a few items. In his collections of data, the mean number of contributions per man is often only two or three. Furthermore, the mean number of "significant" contributions per man is only slightly greater for the men who lived to age 70 than it is for the men who died relatively early.

In order to be included the short-lived man must have produced a significant work at an early age. To qualify for inclusion, a long-lived man was required to produce one significant work but this could have been done either early or late. In other words, in order to achieve a certain degree of eminence, the short-lived man must have fulfilled in a few years what the longer-lived achieved in a more leisurely fashion. We shall show that the consequence of combining data for men of different longevities is a higher average productivity in the early decades.

In this connection Lehman says (p. 4), "Adequate allowance for the unequal numbers of individuals alive at successive age levels was made. . . ." It seems to us that no adequate allowance *can* be made for the fact that all of the significant contributions of short-lived people occur in the early decades, whereas the long-lived can contribute both early and late. In tabulating entries for different decades, the twenties or thirties receive a score for each short-lived person. On the

Submitted for publication December 16, 1955.
Published on a grant from the Forest Park Foundation to the Journal of Gerontology.

other hand, the later decades, such as the sixties, contain no entries for short-lived persons and only part of the entries for the septagenarians. When data from men of different degrees of longevity are included in the same table, the early decades have an inevitable loading which is not shared by the later decades. To give the later decades a similar loading, it would be necessary to adopt the rule of including a long-lived person only if he made a significant contribution in his later years, because, conversely, the short-lived person is included only if he made a significant contribution in the early decades of life. This is a somewhat subtle point, but one which is essential to the correct evaluation of Lehman's data.

From the point of view of the consideration presented above, a very interesting table is presented by Lehman in his penultimate chapter (p. 317). This table represents 1540 notable contributions to various sciences. In this case, the data for persons of different longevity are treated separately. For this reason, the criticism presented above does not apply.

The table shows that for each group the decades of the thirties is most productive but the differences between the thirties and the forties are not large. The largest difference between the thirties and forties occurs among those dying in the forties. In this group ill-health may have contributed to the decrement. For longer-lived groups, even the decrements in the fifties, compared to the thirties, are not dramatic. No group in the fifties drops to the extent which is found when persons are not segregated according to longevity. In other words, this table shows that the combining of data for men of unequal longevity in other tables seems to have exaggerated the apparent age decrement. Nevertheless, even when data refer to men of equal lifespans some age decrement is still found.

This table is so significant in regard to age decrement that it is surprising that Lehman makes no reference to it when discussing the striking decrements reported in his earlier chapters. Nor are its findings adequately reflected in the summary chapter of his book. For these reasons it seems necessary here to emphasize the importance of the data which it contains.

We believe that much of this residual decrement is the product of other deficiencies in methodology. For one thing, it seems likely that the very high peaks of productivity which Lehman reports in his early chapters may be due to errors in sampling and to choosing age-intervals in such a way as to maximize the effects of sampling errors.

Many, but not all, of the curves presented by Lehman are based upon a relatively small number of entries. Thus figure 14 is the result of only 52 entries, figure 16, 30, figure 51, 53, figure 53, 67, and figure 56, 40. These entries are divided among age-intervals, usually 5-year periods, extending from age 20 to age 70 and beyond. With small numbers of entries divided among 10 or more age intervals, one would expect that, even though no true age differences are present, high values in some age-intervals would frequently be obtained through the operation of sampling errors. This fact is important because the highest age score in any body of data is taken as the peak from which decrement is measured. Therefore any exaggeration of the peak naturally results in finding exaggerated decrements.

This factor is further aggravated by the fact that Lehman did not limit himself to a fixed set of age-intervals, but apparently altered them in order to determine the particular "peak years" which seem to characterize a particular set of data. Thus, as the final chapter indicates, the step-intervals for peak years for different activities are variously reported as 22-26, 24-28, 25-29, 26-31, 30-34, 32-36, etc. The modification of age-intervals in order to find "ages of maximum productivity" would be legitimate if the findings were cross-validated against new data, but this was seldom done. Hence the extent to which "peak years" are affected by random errors of sampling is unknown.

There can be little doubt that some part of the decrements reported by Lehman are to be explained by the considerations just presented. The reader of Lehman's book will note that decrements are less precipitous in the graphs which are based upon numerous data and in the construction of which the step intervals follow the decimal system instead of being varied to maximize the peaks.

The preceding arguments have been of a mathematical or statistical sort. Those which follow are of a different kind, but, we think, no less cogent.

Lehman used as a criterion for inclusion of a work as a "significant contribution" the appearance of the work in histories of the appropriate area, or its appearance in lists of "best" books, "best" operas, etc. Perhaps, no better indices of importance are available, but it should be pointed out that these criteria may have certain weaknesses from the point of view of the study of age differences. It is possible that biographies, histories, and lists of best works contain systematic errors somewhat favoring a man's early work at the expense of his later products, and Lehman's findings may reflect these biases. For example, the art historian may be more likely to mention a painter's first significant contribution than he is to mention his last important piece of work. Likewise, an historian of science may be more likely to mention a young man's pioneering research which opened a new vista than he is to describe the subsequent painstaking investigations which were necessary to develop and validate the promise of the pioneering study. It is difficult to know to what extent an apparent age decrement may be due to the proclivities of anthologists and historians rather than to age itself.

In this connection, the possibility of a bias against the evaluation of recent contributions should be considered. It is our impression that critics and historians tend to consider the evaluation of recent contributions to be more difficult than the evaluation of more remote works. They may, therefore, suspend judgment in connection with recent contributions. Now a considerable number of Lehman's subjects were born after 1800 (see chap. 18). Their later works were recent works at the time of the preparation of the source books from which Lehman obtained his data. Unwillingness, on the part of historians and editors, to evaluate recent works would therefore lessen the number of significant works recorded for the later years of some of Lehman's subjects. Consonant with this interpretation is Lehman's report that in former centuries the decrement with age in several fields seems not to have been as great as in recent times (chap. 18). A century or more ago the apparent decline of creativity with age was slight.

Let us note, too, that the assessment of the relative

excellence of work done early and late in a man's career is made exceedingly difficult, if indeed not impossible, by the changes in standards which occur during a man's lifetime. For example, the situation in biology in 1880, when Darwin was 71, was extremely different from what it was when "The Origin of the Species" appeared in 1859 when Darwin was 50. In fact, the difference was due in a large part to Darwin's own work. It seems relatively meaningless to compare biologic contributions made before and after the publication of the theory of evolution. This argument, of course, is not limited to biology. Changing standards characterize all fields, whereas judgments of quality in regard to works separated by several decades seem to imply absolute standards.

Standards for the judgment of quality are further complicated by the great increase in the number of creative workers in most fields which has taken place in recent times. Thus the best psychologist in America in 1900 was the best in a group of approximately 100. The best psychologist today, if he were ascertained, would have to be judged the best among 13,000. A psychologist living in 1900 and still living today, had 99 competitors for distinction in his youth and has 12,999 rivals (or thereabouts) in his later years. Similar, if perhaps less striking, increases in personnel have taken place in other fields. Curves for age changes in number of significant contributions do not, and probably cannot, correct for changes in standards of evaluation which occur during a lifetime.

In summary, we have presented several reasons for scepticism in regard to accepting the view that there is a decrement with age in the production of creative works of high level. We have not attempted to be exhaustive in this treatment. We submit, however, that there is a reasonable doubt that the curves presented by Lehman depict an age decline. Quality of creative work *may* decrease with age, but data presently available do not offer satisfactory evidence.

We would like to be able to suggest a method by which valid conclusions concerning changes in the quality of creative contributions with age could be reached, but we are unable to do so. All sources of data, and all methods of evaluation which we have considered seem to suffer from one or more of the difficulties discussed above. Nevertheless, it has been noted that as the methodologic difficulties in Lehman's work are reduced, the apparent decline with age becomes smaller. Whether ideal data would show no decline prior to extreme old age it is at present impossible to say, but this possibility should not be ignored.

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# REPLY TO DENNIS' CRITIQUE OF AGE AND ACHIEVEMENT

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If Dennis' premises were sound his conclusions also would be sound. Since his premises are largely a result of his misunderstanding and almost completely invalid, his conclusions also are invalid. Let us consider his main points one by one.

Dennis says: "The recent book by Lehman, *Age and Achievement*, seems to indicate that in many fields relatively little creative work of importance is done by persons past 45 or 50 years of age."

My reply: In discussing this topic it is necessary to make a clear distinction between creative *production rate* and total *absolute output*. If Dennis' statement refers to creative *production rate*, the answer would be yes. If, on the other hand, it refers to *total absolute output*, the answer would be no.

In my book I have plainly stated that "if we consider the individual's four or five best works, longer-lived men achieve considerably more high-grade output than do shorted-lived ones." (p. 310).

Dennis says: "That the production of first-rate work in poetry, art, science, and other creative areas decreases markedly with age is a matter of prime importance. If correct, it suggests that the creative worker in many fields should plan for early superannuation."

My reply: The mere fact that the peak production rate occurs early is hardly a sufficient basis for Dennis' assertion that the creative worker should plan for early superannuation. Dennis' statement does not follow logically from my data as he seems to think it does, and to me it does not make sense. Only if *no* masterpieces were produced at older age levels would his inference be justified.

Dennis says: "It is the thesis of this paper that much of the apparent decline in creative achievement revealed by Lehman's tables and graphs is due to factors other than age."

My reply: I would insist that primarily *all* of the decrement is due to factors other than age. The following statement by Fraser which appears in *Age and Achievement* expresses my view very precisely.

"At a meeting of the British Branch of the Club for Research on Aging, held in London, July 16, 1946, Fraser asserted that clinical research on physiological aging is practically impossible at the present time. This is due to the fact that there are always many uncontrolled variables to consider. Because in old age pathological conditions are so generally present, in addition to the old age itself, Fraser suggested that it would be better for clinicians to concentrate on studying primarily the pathological conditions themselves rather than to attempt clinical study of the age factor alone." (p. 116ff.)

Surely, the aging process never occurs without the accompaniment of numerous changes other than the age change. Certainly, it is *not age per se* but rather the innumerable factors that accompany age change that produce the decrement in my age-curves.

Dennis says: " . . . it is not incorrect to say that Lehman has been interested primarily in determining the 5 or 10 year age-period in which important creative works have been most often produced."

My reply: I have also been interested in the creative production rate for the entire lifespan, and not only for the most important works but also for contributions of relatively minor importance.

Dennis says: "To avoid introducing a bias of his own, he always uses a list of works drawn up by some other person."

Submitted for publication May 12, 1956.

My reply: The chronologies that I have employed were prepared not merely by some other person but rather by recognized specialists in each specific field. In selecting these chronologies I did not select them merely on the basis of my own judgment. Always I had the help of the best advisers I could find.

Dennis says: "In most instances, as presented by Lehman, the decrements are very striking."

My reply: In my book I pointed out that the decrements are also gradual. Note my published statements with reference to this point.

"The decline is gradual at all the older ages—much more gradual than its onset. Indeed, the decrement is so gradual that one cannot place the maximum rate of production for chemists at any one specific year with assurance." (p. 6)

In the final chapter of my book I repeat that warning.

". . . the rate of good production usually does not change much in the middle years and the decline, when it comes, is gradual at all the older ages." (p. 326)

Dennis says: "Examination of such findings, page after page, creates an impression of inevitable decline."

My reply: The words "inevitable decline" are Dennis' words—not mine. There is no evidence that the decline is inevitable.

Dennis says: "If these charts are taken at their face value, we must conclude that in most kinds of creative work the output of work of first rate quality is greatly reduced after the thirties."

My reply: This statement is correct only if Dennis is speaking of *production rate*. It is erroneous if he refers here to total absolute output beyond the thirties. The median chronologic ages in my tables reveal that (roughly) about half of the total of the most significant creative contributions appear beyond age 40!

Dennis says: "A major methodologic weakness in Lehman's treatment of data lies in the fact that in most instances a table or graph combines information pertaining to men of different degrees of longevity."

My reply: I do not regard this as an example of "methodologic weakness" at all. In the words of John E. Anderson, "methodologic weakness" consists not so much in the use of a particular method as in the failure to use a more adequate method for the problem in hand when such a method is available. In his critique Dennis fails to suggest a more adequate method and I have yet to find one.

Dennis argues here that the decline in production rate as revealed by my age-curves is steeper than it should be owing to the fact that some of the creative workers died early. I do not see that this point weakens my findings in any way. My data are pretty convincing that, even if *all* of the creative workers had been long-lived, the relative creative production rate of the old-sters would not have been as great as that of the younger men.

One need not deplore, in so many words, the fact that some of them died young. This fact is too obvious to merit comment. My curves imply, among other things, that, since a man can die young, the young man had better get started on his creative career early for he may die early whether his production rate be large or small, or whether his maximum production rate is most likely to occur early or late.

Dennis says: "We shall show that the consequence of combining data for men of different longevities is a higher average productivity in the early decades."

My reply: The error introduced by this factor is very slight. This statement is supported by data presented in my book. For example, figure 55 (p. 79) sets forth the creative production rate for the one best oil painting by each of 61 artists, each of whom lived to 70 or beyond. Figures 53 and 54 (p. 78), on the other hand, set forth the creative production rate for *all* major and minor painters in oil for whom age data were available. Some members of the latter two groups were short-lived and some of them were long-lived. It will be noted that the three figures 53, 54, and 55 differ very slightly.

I also would call Dennis' attention to figure 9 (p. 15) which presents age data for chemists. The dash line of this figure gives a fair estimate regarding the output that could have been expected to occur at the older age levels if the short-lived chemists had all lived to age 80 and had contributed during their older years at the same rate as did the long-lived chemists of corresponding age levels. In figure 9 it will be noted that the solid line, which sets forth data both for short-lived and for long-lived chemists, differs only slightly from the dash line which presents the output that could have been expected to occur if all of the chemists had been long-lived.

Dennis' argument would be more cogent if many of our greatest creative thinkers had died young. Actually, and contrary to popular opinion, geniuses do not die young. My own unpublished tabulations show this clearly. So also do Armattoes' data (1, p. 391). With some dramatic exceptions, our greatest creative thinkers have been rather long-lived (See fig. 10, p. 17, of *Age and Achievement*).

Dennis says: "We shall attempt to show that this method of treating data acts in part to produce the productivity differentials which Lehman discovers. . . .

"This is a somewhat subtle point, but one which is essential to the correct evaluation of Lehman's data."

My reply: When I prepared my book manuscript I believed (and I still believe) that I covered this point rather thoroughly. I said (p. 316) that table 58 reveals the percentages of total output contributed during successive decades by men of varying longevity, and in commenting upon this table, I wrote as follows:

"In this table the maximal rate of output for each sub-group is italicized, and the italicizing occurs always at 30 to 39. This table reveals that, on the whole, the greater the number of decades lived, the smaller the percentage of the sub-group's total output contributed from 30 to 39. Notice, for example, that, whereas those who died prior to 50 contributed 50 per cent of their total output from 30 to 39, those who died at 85 or beyond contributed only 29 per cent of their total at 30 to 39. This finding results from the simple arithmetical fact that when total life output is partitioned into a larger number of fractional parts, each fractional part tends to become a smaller proportion of the total." (p. 316)

I say later with reference to this table:

"It is a matter of common knowledge that, within recent times, the mean length of life in the U.S.A. has been increasing and that it will probably continue to increase in the immediate future. My findings suggest that, if this current trend continues, the following other results are also likely to ensue; (1) The total creative output of groups of creative workers will increase somewhat, the exact amount of the increase varying inversely with the quality of the output under consideration. (2) Achievements will be made over a wider span of years; hence (3) Mean age at time of achievement will be somewhat older. (4) A smaller percentage of man's total creative output will occur from 30 to 39. (5) Since the maximal rate of output for creative achievements of highest quality has occurred heretofore most often during the thirties both for long-lived and for short-lived groups, 30 to 39 probably will continue in future years to be man's most fruitful decade for creative work of greatest merit. Certainly, it will require something more than a mere increase in longevity to alter this." (p. 322)

Dennis seems to have gotten his point from chapter 15 of *Age and Achievement*. Surely it would not be too much to expect other readers to make the same deduction either by study of table 58 or by study of my statements with reference thereto.

Dennis says: "To give the later decades a similar loading, it would be necessary to adopt the rule of including a long-lived person only if he made a significant contribution in his later years, because conversely, the short-lived person is included only if he made a significant contribution in the early decades of life."

My reply: This suggestion permits several interpretations. If Dennis means to suggest that I should include long-lived contributors if they made significant contributions *only* during their later years (excluding those who contributed both early and late in life), this procedure obviously would yield age-curves with maximum production rates at elderly ages. If, on the other hand, he means that I should include long-lived individuals if they made significant contributions *both* during their young years *and also* during their later years, this plan would yield age-curves rectangular in shape.

Does Dennis really mean to say that either of the foregoing measures would be an improvement upon the procedure that I employed? I think either of his plans would result in more rather than in less error in the age-curves.

Dennis says: "From the point of view of the consideration presented above, a very interesting table is presented by Lehman in his penultimate chapter (p. 317)."

My reply: In his interpretation of table 58 (p. 317) Dennis seems to regard the very gradual decrement in the percentages of output contributed by the sub-group which lived to be age 85 or beyond as an inevitable and inescapable phenomenon. This is not the case at all. Although in table 58 (p. 317) the modal value for the sub-group dying prior to age 50 differs greatly from the modal value for the sub-group living to age 85 or beyond, other tables could easily be prepared with modal values of much more nearly the same magnitudes.

These latter tables could be obtained by doing two things: (a) Excluding the contributions of creative workers born prior to about 1775, and including only the contributions of men born from about 1775 to 1850, (b) Employing only tabulations which exhibit a very marked decrement in production rate beyond age 40.

Dennis says: The largest difference between the thirties and forties occurs among those dying in the forties. In this group ill-health may have contributed to the decrement."

My reply: Dennis seems to think that dying before 50 is the same as "dying in the forties." This is, of course, erroneous. The group dying before 50 started to dwindle at age 21. Well over a third of them died prior to age 40. And during the forties they passed away so rapidly that, as compared with age group 30-39, less than half as much manpower was available to contribute at ages 40-49. Ill-health may have contributed to the large drop in the percentage of total output from ages 30-39 to ages 40-49, but early mortality was probably an even more important factor.

Dennis says with reference to table 58 (p. 317): "This table is so significant in regard to age decrement that it is surprising that Lehman makes no reference to it when discussing the striking decrements reported in his earlier chapters. Nor are its findings adequately reflected in the summary chapter of his book. For these reasons it seems necessary here to emphasize the importance of the data which it contains."

My reply: Dennis overinterprets this table and perhaps I may be partly to blame for it. I published only one table of that nature and I did not explain in detail just how the age data were obtained. Table 58 (p. 317) includes data for 10 different groups of scientists, many of whom were born two or three centuries ago. If I had employed other data than those that I used in constructing figure 58 the percentage of output for the long-lived sub-group at ages 30-39 could have been greater and the decrement at the older age levels could have been more rapid.

To obtain a comprehensive picture of the over-all facts, figure 58 (p. 317) is insufficient. I did not publish more tables similar to figure 58 because of the cost. Although in my book as a whole I presented representative and *not* one-sided data, I could *not* publish all of my findings for financial reasons. Had I tried to do so the cost of publishing my manuscript would have been prohibitive. As it was several commercial publishers refused to accept my manuscript for financial reasons and I was obliged to spend several years (with the aid of some kind and influential friends) looking for a sponsor willing to subsidize it.

In the form in which it finally appeared, the cost of publishing my book was so great that several chapters had to be deleted in order to reduce the cost of publication to a reasonable sum. Without those deletions I might not have been able to find a sponsor at all.

Dennis says: ". . . it seems likely that the very high peaks of productivity which Lehman reports in his early chapters may be due to errors in sampling and to choosing age-intervals in such a way as to maximize the effects of sampling errors."

My reply: The sharpness of some of the peaks in my age-curves is certainly due in part to the manner in which I chose my age intervals. This was fully explained in my book. But when one, by this means, can obtain the same sharply pointed peaks in age-curve after age-curve, surely something other than chance factors must be operating.

Dennis emphasizes the likelihood of sampling errors by remarking: "Many, but not all, of the curves presented by Lehman are based upon a relatively small number of entries."

My reply: It is one thing to say that a finding may be due to sampling error when the number of cases is small. But it is quite another thing to say that this can be checked *only* by cross-validation *within the same specific group*, e.g., checking the sampling error for chemists with another group of chemists. It seems to me that, quite apart from the fact that I did cross-validate my data in this way whenever possible (I have data for 5 chronologies of chemistry contributions, for example) the consistency of the age-levels at which maximum production rate occurred *among different fields of endeavor* is so great that this constitutes a very real refutation of Dennis' emphasis on the sampling error.

Dennis says: "Lehman did not limit himself to a fixed set of age-intervals, but apparently altered them in order to determine the particular 'peak years' which seem to characterize a particular set of data."

My reply: May I suggest that Dennis try to assemble age data for creative contributions of highest merit and then that he try to choose age-ranges for his class-intervals so as to obtain maximum production rates beyond age 45 or 50? I do not believe that he will succeed in doing it, and if I am still among the living when he achieves that goal, I shall be greatly interested in his findings.

Dennis says: "The modification of age-intervals in order to find 'ages of maximum productivity' would be legitimate if the findings were cross-validated against new data, but this was seldom done. Hence the extent to which 'peak years' are affected by random errors of sampling is unknown."

My reply: If chronologist "A" makes out a list of the greatest contributions to the field of chemistry that the western world has known, and if chronologist "B" makes out another list of the same type of contribution, the overlapping is very great. If one constructs a separate age-curve for each list of contributions (and I have done this repeatedly for various fields of endeavor) it is hardly sound to regard "B's" list as "new data,"

because the overlapping is so great. Just what does Dennis mean by "new data"? In making my studies I partitioned my data in about every way that seemed feasible. Would Dennis want me to publish all of these comparisons and cross-comparisons which lead only to the same conclusions and, if so, at whose expense?

Dennis says: "The reader of Lehman's book will note that decrements are less precipitous in the graphs which are based upon numerous data and in the construction of which the step intervals follow the decimal system instead of being varied to maximize the peaks."

My reply: Those of my graphs which are based on large numbers of cases reveal production rate for mere quantity of output rather than for output of greatest significance. I think the slow decrement in such age-curves is due more to that fact than to anything else. Such curves tend to have no definite peak. In drawing them I did not try to maximize the peak simply because there was not much of a peak to be maximized.

Dennis says: "It is possible that biographies, histories, and lists of best works contain systematic errors somewhat favoring a man's early work at the expense of his later products, and Lehman's findings may reflect these biases."

My reply: This statement is purely speculative. Nor do I see how the validity of this point could be proved.

Dennis says: ". . . an historian of science may be more likely to mention a young man's pioneering research which opened a new vista than he is to describe the subsequent painstaking investigations which were necessary to develop and validate the promise of the pioneering study."

My reply: I tried in my investigations only to ascertain the ages at which the most significant creative contributions were made. I did *not* attempt to ascertain how many years it took the contributor to sell his great idea to his colleagues. This latter task would be well-nigh impossible and certainly would require an enormous amount of labor. One man alone could hardly do it.

Dennis says: "Now a considerable number of Lehman's subjects were born after 1880 (see chap. 18)."

My reply: This statement is exactly 100 per cent wrong as regards chapter 18 and I simply do not understand how such a careful worker as Dennis could make such a gross blunder. In preparing chapter 18 *not one* contribution was employed that was made by any individual born subsequent to 1880. And not more than 1 or 2 per cent of the contributions employed in the preparation of chapter 18 were made by men born subsequent to 1850.

When Dennis reviewed my book for the *Psychological Bulletin*, I assumed, of course, that he had read the book. Upon reading this critique I am led to wonder whether that assumption was well-founded. Certainly, if he actually did read *Age and Achievement*, he must have read it very selectively, rather than objectively.

I suggest that Dennis read chapter 18 again, noting the legends beneath the several paragraphs and looking up the birth dates of the noted men listed in table 54 (p. 303), table 55 (p. 304), and table 56 (p. 306). I believe that he is due for a surprise.

Dennis says: "Consonant with this interpretation is Lehman's report that in former centuries the decrement with age in several fields seems not to have been as great as in recent times (chap. 18). A century or more ago the apparent decline of creativity with age was slight."

My reply: The second of the foregoing statements is incorrect. For men born *from about 1755 to 1850*, the decrement in production rate at the uppermost age levels is very great for work of highest quality. For men born prior to about the year 1775, on the other hand, the decrement at the older age levels is much more gradual. Dennis seems to have misinterpreted the words "then" and "now" which appear in the title of chapter 18.

Dennis says: "It seems relatively meaningless to compare biologic contributions made before and after the publication of the theory of evolution. . . . Changing standards characterize all fields, whereas judgments of quality in regard to works separated by several decades seem to imply absolute standards."

My reply: It seems to me that this question had best be left to specialists within the various fields of endeavor to decide. It is not a question that can be settled by Dennis and/or Lehman.

Dennis says: "Curves for age changes in number of significant contributions do not, and probably cannot, correct for changes in standards of evaluation which occur during a lifetime."

My reply: To me this argument is wholly irrelevant. The chronologies that I employed list presumably the most important achievements that have ever been made. In this sense each contributor was competing not merely with others of his own generation but with *all of the contributors who ever lived.*

Even if it be granted for the sake of argument that this statement might possibly hold true for some fields of endeavor, it certainly does not apply to all of my work. For example, I identified the most important philosophic treatises by canvassing more than 50 standard books which deal with the history of philosophy. (The 50 histories were selected with the aid of professional philosophers. I did not select them unaided). The foregoing procedure assumes that those philosophic writings which were cited and discussed by more historians probably possess greater merit than do those which were mentioned and discussed by fewer historians.

In this instance each philosopher's several treatises were being compared not with the works of others but with the given individual's own earlier and later works. Regardless of what Dennis may say, I think this a valid procedure and I have found that the professional philosophers with whom I have discussed the matter agree with me on this point.

Dennis says: "In summary, we have presented several reasons for scepticism in regard to accepting the view that there is a decrement with age in the production of creative works of high level."

My reply: If this statement refers to creative production rate for work of the greatest significance, I disagree most vehemently. I would even insist that my book understates rather than overstates the case for youth. This is because of the factor of time-lag between dates of achieving and dates of publication which sometimes caused me to credit achievements to age groups older than was warranted by the actual facts in the case. In this connection I would call Dennis' attention to the footnote which discusses time-lags—at the bottom of page 10 in *Age and Achievement.*

Dennis says: "Whether ideal data would show no decline prior to extreme old age is at present impossible to say, but this possibility shou'd not be ignored."

My reply: Can Dennis really be serious? Does Dennis refer also to decline in athletic achievement? Does he include achievement in the field of physics? I wonder if he happened to see the film which recently has been exhibited so widely and in which Edward R. Murrow interviewed Dr. Robert Oppenheimer with reference to some things scientific? In this interview Murrow at one point asked Oppenheimer if it were true that great scientists have often done their most important work at

early ages. To this query Oppenheimer replied that this certainly has been true in the field of physics. Oppenheimer then illustrated his point by reference to the work of Sir Isaac Newton. According to Oppenheimer Newton did all or almost all of his really important work at age 22. (In my book credit for Newton's *Principia* was given to age groups 45-49 because Newton's *Principia* was published when Newton was 45).

Although Oppenheimer probably never has heard of either me or my book, *Age and Achievement*, he seems to agree with me that most great physicists have achieved their maximum production rate for their most significant contributions at fairly early ages. I believe that Oppenheimer is right in this opinion and that Dennis is wrong.

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# BOOK REVIEWS

CHARTER FOR THE AGING, Report on the New York State Conference on Problems of the Aging, Office of the Special Assistant, Problems of the Aging, State Capitol, Albany, New York, 1956, 659 pages, $3.00.

*Charter for the Aging* is a report of the New York State Governor's Conference on Problems of the Aging held in October, 1955, together with Governor Harriman's special message to the Legislature on problems of the aging, January 18, 1956.

The book contains the few introductory and concluding speeches that were made, papers prepared for each of the 11 Conference Committees, the Committees' conclusions and recommendations, and the Governor's Special Message. The Conference Committees represented: Community Organization; Education and Recreation; Employment; Group Care; Health, Medical Care and Rehabilitation; Housing; Income Maintenance and Prevention of Indigency; Mental Health; Retirement Policies; Religion; and University Research, Teaching and Training.

A great deal of preliminary work was done in the summer before the Conference convened by authorities who served as consultants. Many of them are well known for their work and interest in the field: Raymond Kuhlen, Harry Levine, John McConnell, Louis Dublin, Geneva Mathiasen, and Albert Abrams—to mention only a few. They collected, analyzed, and prepared information and data that were placed in the hands of each conferee in advance of the Conference, and one or more consultants worked with each of the 11 Conference Committees. Each of the state departments represented on the Governor's Inter-Departmental Committee on Problems of the Aging: Civil Service, Commerce, Education, Insurance, Health, Housing, Labor, Mental Hygiene, Social Welfare, and Workman's Compensation, provided staff services before and during the Conference.

Governor Harriman, in his opening address, set the stage for one of the most productive state conferences on aging that has ever been held when he said he wished its deliberations to lead to practical proposals for action. In announcing the Conference in June he stated its 4 primary purposes to be: 1) a "grass-roots" view of the needs of older persons; 2) help in developing programs in the several fields; 3) advice as to areas of responsibility belonging to private and public agencies; and 4) counsel on the respective roles of state and local governments, either through legislation or administrative effort. That he was seriously interested in what was taking place and that he had followed its activities very closely were demonstrated in his speech at the conclusion of the Conference, commenting on the particular recommendations each of the committees had made. But the Governor's real interest, and especially his concern for definite action to be taken, was shown in his special message to the Legislature which followed three months later in which he made more than a score of specific recommendations, some involving special legislation, others providing for expanded budgets in certain departments and divisions to enable them to undertake new services.

One expects New York State, which has been in the lead so long in its interest and activities for the aging, to produce a memorable document, and it has. One is impressed with the expertness and organization of the Conference and the desire on the part of the officials, especially the Governor, to get things done.

The title of the book, *Charter for the Aging*, is in no way misleading for its recommendations do constitute a real charter. It will have its effect not only in New York State, but in the 47 other states. The Charter follows by only 8 months the significant publication of the Council of State Governments, *The States and Their Older Citizens*, a report of the Governors' Conference setting forth a bill of objectives for older people and a 15 point program for action in the field of aging. They are both most important documents and will have tremendous influence in improving the lot of the older person.

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Books received since April 1 are acknowledged in the following list.

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*Aged and Aging in Illinois*, Part II—the Mentally Deficient, Research Study 68-2, by Otto L. Bettag, David Slight, Phillip W. Wenig, and William H. Sorensen. The Department of Public Welfare, 1955, 54 pages, multilithed, paper bound.

*Charter for the Aging*, a Report of the New York State Conference Convened by Governor Averell Harriman at the State Capitol in Albany, 1956, 659 pages (reviewed in this issue, page 338).

*Government Payments to the Aged or for Their Public Care in the State of New York, in the Past, at Present, and a Decade Ahead*, by Sidney G. Tickton. The Seventh Company, Inc., New York, 1956, 87 pages, paper bound.

*Migration and Mental Disease*, by Benjamin Malzberg and Everett S. Lee. Social Science Research Council, 230 Park Ave., New York, 1956, 142 pages, paper bound, $1.50.

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JOURNAL OF GERONTOLOGY

VOLUME 11, NUMBER 3
JULY, 1956

# Section C

## Index to Current Periodical Literature

# INDEX TO CURRENT PERIODICAL LITERATURE

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THE SUBJECT categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus, most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given (*B.A.—Biological Abstracts: P.A.—Psychological Abstracts*, and *P.I.—Population Index*). Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the Years 1900-1933*, 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Branch, Baltimore City Hospitals, Baltimore 24, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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